COMPOUNDS AND METHODS FOR THE TREATMENT OF ASTHMA

Field of the Invention

[0001] The invention relates to compounds and methods for the treatment of asthma. The methods involve mast cell stabilization together with selective inhibition of iNOS. The compounds are combinations of a mast cell inhibiting moiety and an inhibitor of iNOS.

Background of the Invention

[0002] Asthma is a chronic airway inflammatory disorder characterized by bronchial hyper-reactivity and bronchospasm, among other abnormalities. Lungs of asthmatic patients have increased numbers of inflammatory cells in bronchioalveolar fluid and in lung tissues. These inflammatory cells include eosinophils, basophils, neutrophils, macrophages, and lymphocytes. In asthmatic lungs, the epithelium, including ciliated columnar epithelial cells, is damaged. IgE-antigen-mast cell interactions represent the early molecular and cellular events that cause inflammatory conditions of asthma.

[0003] Mast Cell Stabilizing Agents provide one approach to the prophylaxis and/or treatment of asthma. The prototype drug, disodium cromoglycate was synthesized in 1965 and was approved in the United States in 1973 as a prophylactic, nonbronchodilating anti-inflammatory drug for the therapy of allergic disorder. Cromolyn is an odorless, white, hygroscopic crystalline powder that is freely soluble in water up to 5%. Animal and human studies show it to be excreted unchanged in bile and urine. When inhaled into the pulmonary tree, as for treatment of asthma, only about 8% of a dose is deposited in the lung and absorbed. Peak plasma levels occur within 15 minutes, the biologic half-life is 46-99 minutes. Oral administration in humans results in approximately 1% being systemically absorbed. Cromolyn toxicity studies show an impressively low order of acute toxicity, and adverse effects

tend to be minimal and reversible. Cromolyn has a unique, purely prophylactic action with no intrinsic bronchodilator or antihistaminic activity. Nedocromil was introduced subsequent to cromolyn. It is the other standard mast cell stabilizer used in the treatment of asthma. Its chemical properties and therapeutic characteristics are similar.

[0004] Nitric oxide (NO) is a diffusible radical involved in many physiological and pathological processes. It is synthesized *in vivo* by oxidation of L-arginine. The synthesis is catalyzed by a family of enzymes known as nitric oxide synthases or NO-synthases (NOSs), which are referenced in the international enzyme nomenclature system under the number E.C.1.14.13.39. Three NOS isoforms, two of which are constitutive and one inducible, are known:
(1) A neuronal NOS (NOS-1 or nNOS) was originally isolated and cloned from nerve tissue in which it is a constitutive enzyme. nNOS produces NO in response to various physiological stimuli, such as the activation of membrane receptors, according to a mechanism dependent on calcium and on calmodulin. nNOS-derived NO serves as a neurotransmitter.
(2) An inducible NOS (NOS-2 or iNOS) can be induced in response to immunological stimuli such as, for example, cytokines or bacterial antigens in various cells such as, for example macrophages, epithelial cells, hepatocytes, glial cells, and other cell types. The activity of this isoform is not regulated by calcium. Once induced, it produces large amounts of NO over prolonged periods.
(3) An endothelial NOS (NOS-3 or eNOS) is constitutive and calcium/calmodulin-dependent. It was originally identified in vascular endothelial cells, in which it generates NO in response to physiological stimuli such as the activation of membrane receptors.

[0005] Nitric oxide produced by eNOS and nNOS plays a critical role in cellular signaling and acts to control numerous physiologic functions including vasodilation and bronchodilation in the lung. In the asthmatic lung, eNOS and nNOS are downregulated, and thus contribute to edema and bronchoconstriction. Contemplating the problem of inadequate eNOS and nNOS activity, in an approach

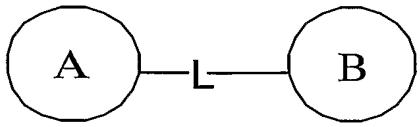
which is the opposite of that taken in the present invention, Garvey et al. (US published application 2003/0199529) have attached stimulators of endogenous NO production to mast cell inhibitors.

[0006] The NO produced in large amounts by the inducible isoform iNOS is involved in pathological phenomena associated with acute and chronic inflammatory processes in a large variety of tissues and organs. NO is highly reactive and, together with superoxide, forms peroxynitrite which damages tissues. In asthma this results in epithelial cell extrusion, sloughing, and cessation of cilia function. An excessive production of NO by induction of iNOS thus plays a part in degenerative pathologies with inflammatory components, such as asthma.

[0007] In conditions in which an overproduction of NO is deleterious, it would be desirable to reduce the production of NO by administering substances capable of inhibiting iNOS. However, given the important physiological roles played by the constitutive isoforms, selective inhibition of iNOS is required.

Summary of the Invention

[0008] In a composition aspect, the invention relates to agents for treating a pulmonary disorder represented by the structure:



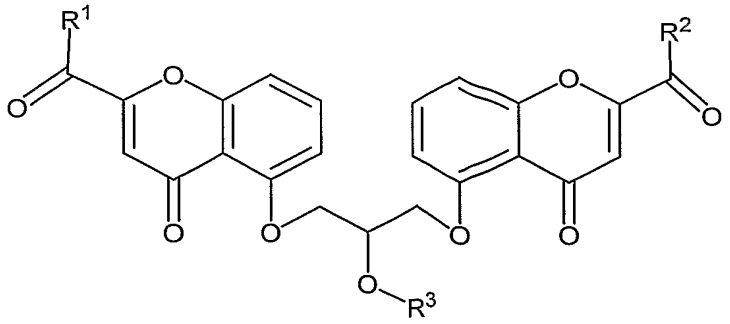
wherein

A is a mast-cell stabilizer;

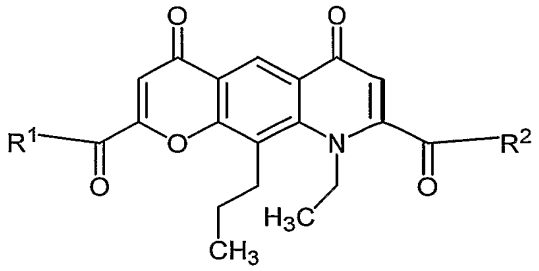
L is a covalent linkage;

B is an iNOS inhibitor.

[0009] Examples of such agents are compounds of formula I or II



I



II

wherein

R^1 and R^2 are chosen from hydroxy, C_1, C_2, C_3, C_4, C_5, and C_6 straight and branched alkoxy, -G-O(C=O)R^4, R^5, -NHR^6, -OR^7 and -$O^- X^+$, wherein X^+ is a pharmaceutically acceptable cation;

R^3 is chosen from hydrogen, -(C=O)R^4, -(C=O)-G-O(C=O)R^4, -(C=O)R^5, -(C=O)NHR^6 and -(C=O)OR^7;

-O(C=O)R^4 is the deshydrogen residue of a carboxylic acid, the parent of which, R^4COOH, is an inhibitor of inducible nitric oxide synthase (iNOS);

-(C=O)R^4 is the deshydroxy residue of a carboxylic acid, the parent of which, R^4COOH, is an inhibitor of iNOS;

R^5 is -O-R^{20}-U, wherein U is chosen from hydrogen, (1,2-dithiolan-3-yl) and phenyl, and R^{20} is a divalent C_1 to C_{20} alkane or oxaalkane residue;

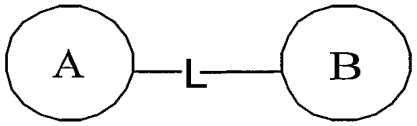
-NHR^6 is the deshydrogen residue of an amine, the parent of which, R^6NH_2, is an inhibitor of iNOS;

-OR^7 is the deshydrogen residue of an alcohol, the parent of which, R^7OH, is an inhibitor of iNOS;

G is a linking moiety cleavable under physiologic conditions. In the compounds of the invention, at least one of R^1, R^2 and R^3 must be -G-O(C=O)R^4, -R^5, -NHR^6, -OR^7, -(C=O)R^4, -(C=O)-G-O(C=O)R^4, -(C=O)R^5, -(C=O)NHR^6 or -(C=O)OR^7.

[0010] In another composition aspect, the invention relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a compound as described above.

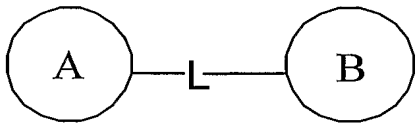
[0011] In a method aspect the invention relates to a method for treating a pulmonary disorder comprising administering a compound represented by the structure:



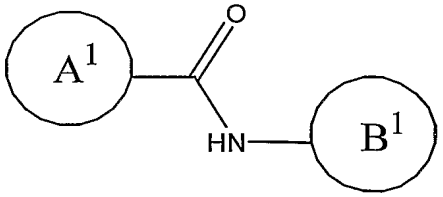
[0012] In a second method aspect, the invention relates to a method for treating a pulmonary disorder comprising co-administering a mast-cell stabilizer and an iNOS inhibitor in the form of a salt, in which one of the mast-cell stabilizer and the iNOS inhibitor is a cation or dication, and the other is an anion or dianion.

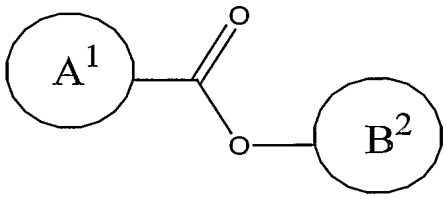
Detailed Description of the Invention

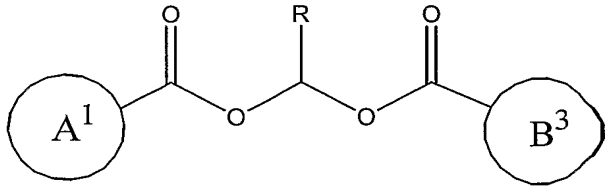
[0013] Agents for treating a pulmonary disorder according to the invention are represented by the structure:

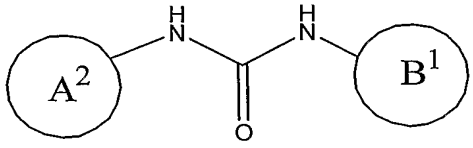


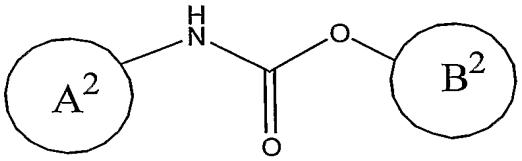
[0014] In one embodiment, L is chosen from -CONH-, -COO-, -O(C=O)O-, -O(C=O)NH-, -NHCONH- and -(C=O)OCH(R)O(C=O)- and the compound is represented by a structure chosen from:

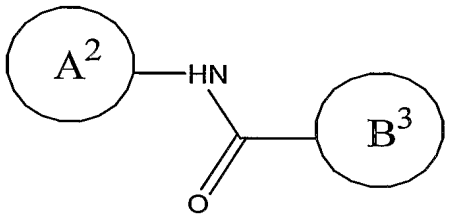


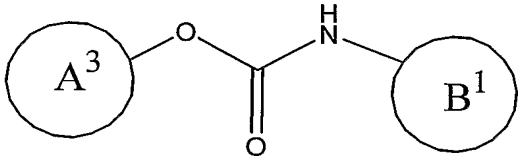


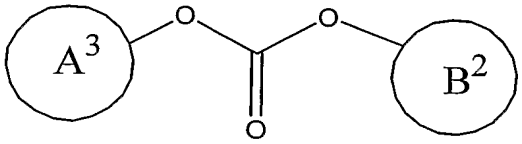


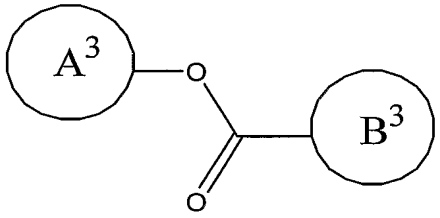










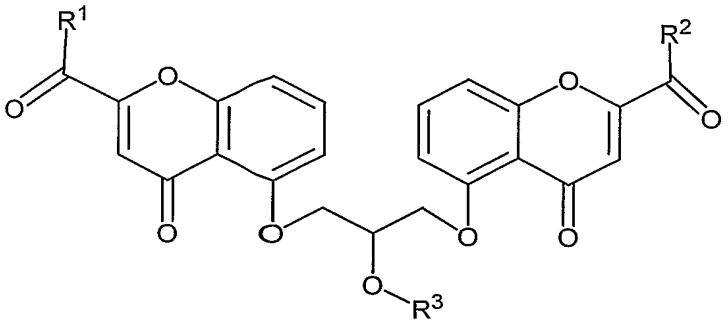


and

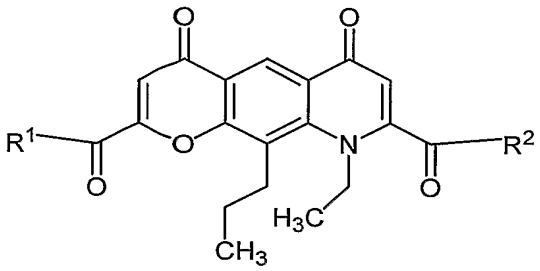
in which A^1 is a mast-cell stabilizer having a carboxylic acid substituent; A^2 is a mast-cell stabilizer having an amine substituent; A^3 is a mast-cell stabilizer having an alcohol substituent; B^1 is an iNOS inhibitor having an amine substituent; B^2 is an iNOS inhibitor having an alcohol substituent; B^3 is an iNOS inhibitor having a carboxylic acid substituent; and R is hydrogen or methyl. Cromolyn would be an example of a compound that fell into the categories A^1 (a mast-cell stabilizer having a carboxylic acid substituent) and A^3 (a mast-cell stabilizer having an alcohol substituent). Nedocromil would be an example of a compound that fell into category

A^1. Numerous examples of compounds that fall in categories B^1, B^2 and B^3 are shown below as examples of parents of R^4.

[0015] In a particular embodiment, the compound is of formula I or II



I



II

In these compounds

R^1 and R^2 are chosen from hydroxy, C_1, C_2, C_3, C_4, C_5, and C_6 straight and branched alkoxy, -G-O(C=O)R^4, R^5, -NHR^6, -OR^7 and -O^- X^+, wherein X^+ is a pharmaceutically acceptable cation;

R^3 is chosen from hydrogen, -(C=O)R^4, -(C=O)-G-O(C=O)R^4, -(C=O)R^5, -(C=O)NHR^6 and -(C=O)OR^7;

-O(C=O)R^4 is the deshydrogen residue of a carboxylic acid, the parent of which, R^4COOH, is an inhibitor of inducible nitric oxide synthase (iNOS);

-(C=O)R^4 is the deshydroxy residue of a carboxylic acid, the parent of which, R^4COOH, is an inhibitor of iNOS;

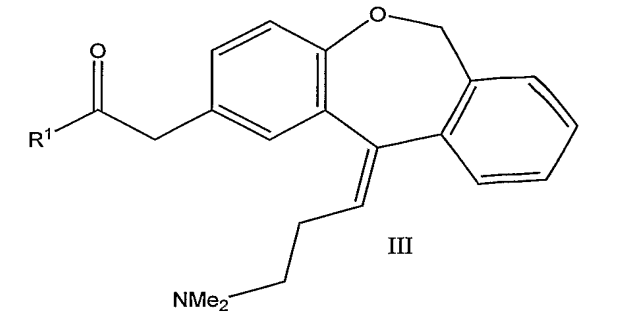
R^5 is -O-R^{20}-U, wherein U is chosen from hydrogen, (1,2-dithiolan-3-yl) and phenyl, and R^{20} is a divalent C_1 to C_{20} alkane or oxaalkane residue;

-NHR^6 is the deshydrogen residue of an amine, the parent of which, R^6NH_2, is an inhibitor of iNOS;

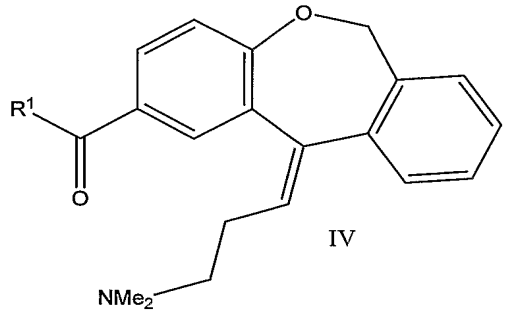
-OR^7 is the deshydrogen residue of an alcohol, the parent of which, R^7OH, is an inhibitor of iNOS;

G is a linking moiety cleavable under physiologic conditions.

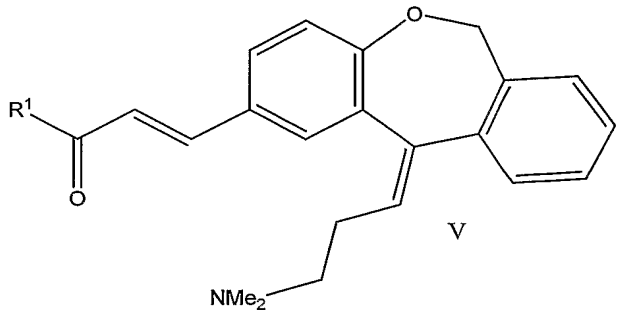
Additional examples of such compounds include structures III through XI in which the R-groups retain the above definitions and R^{10} has the same definition as R^1 and R^2:



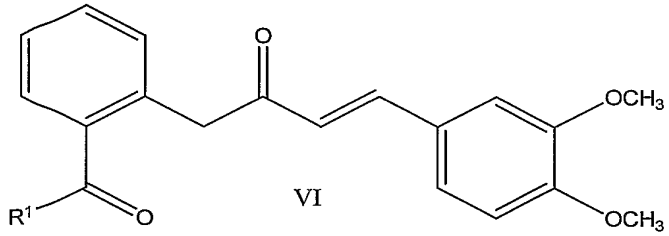
III



IV



V



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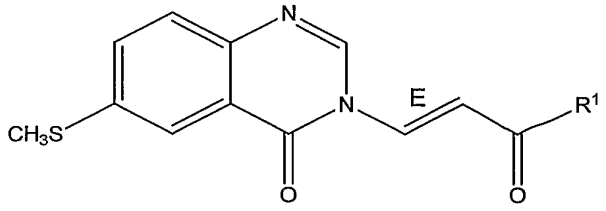
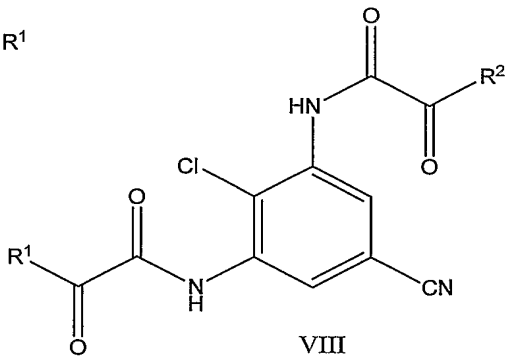
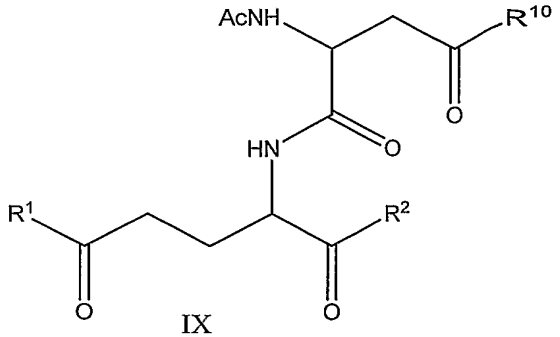


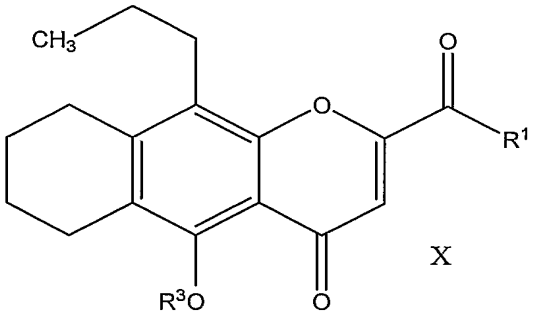
VII



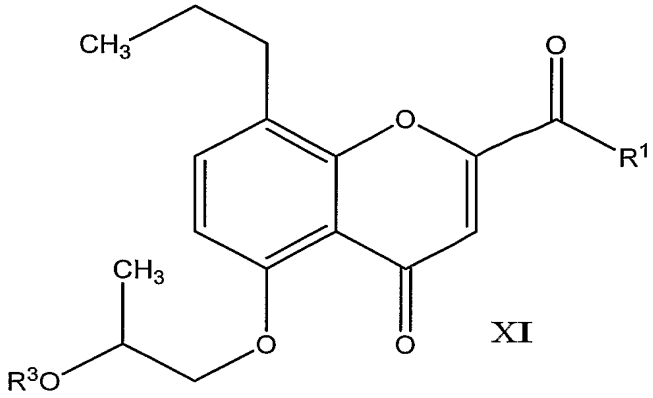
VIII



IX

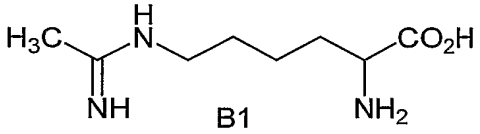


X

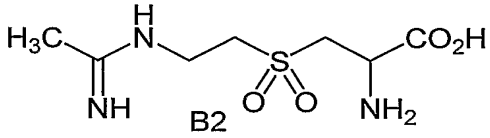


XI

[0016] Parents of the formulae R^4COOH and R^6NH_2 include:



B1



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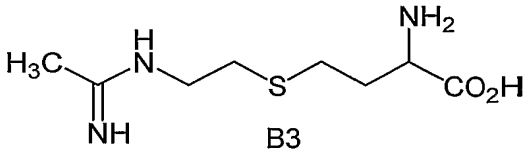

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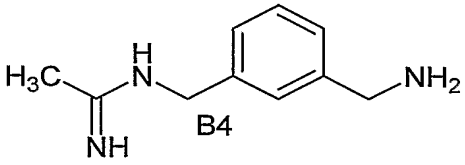

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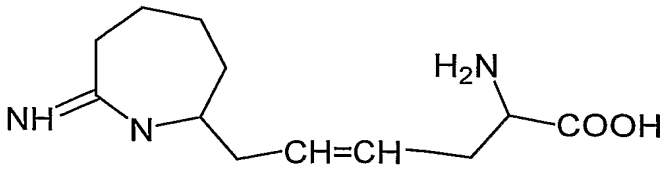

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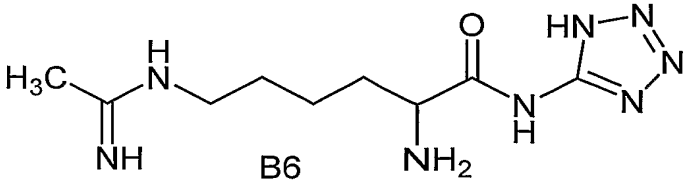

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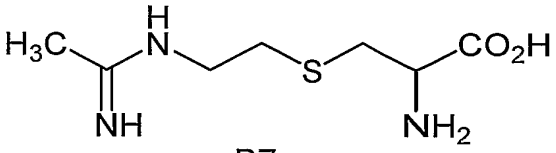

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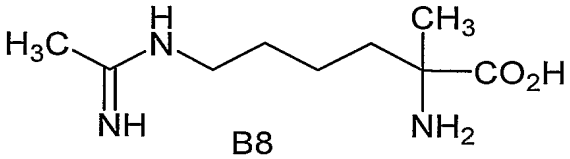

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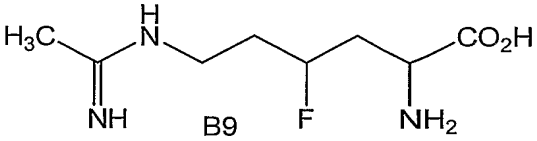

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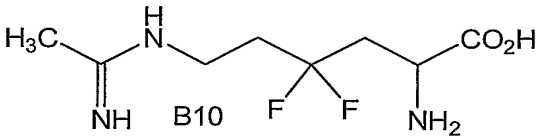

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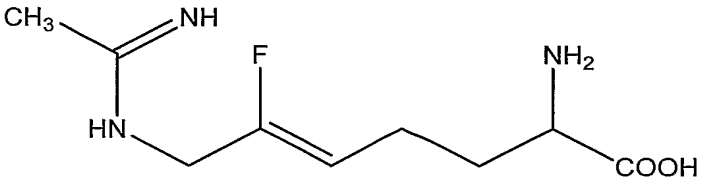

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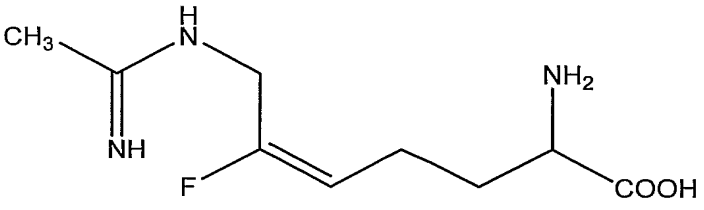

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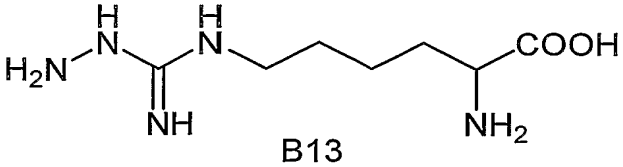
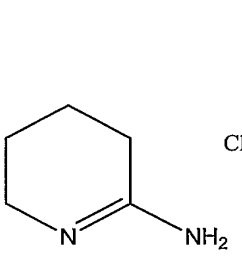


B13

and

Additional parents R^6NH_2 may be chosen from compounds of structure:



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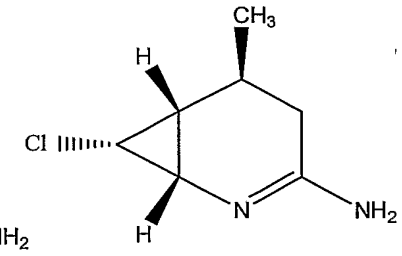
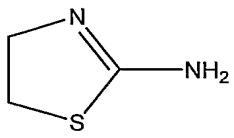


B15



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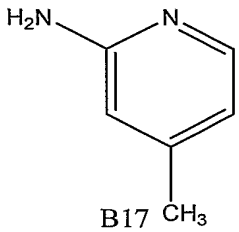
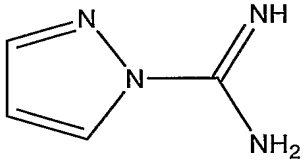
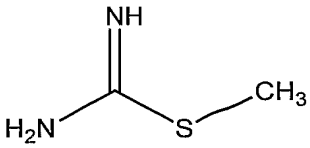


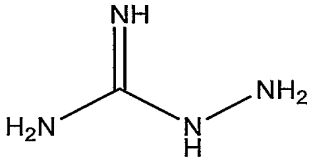
B17



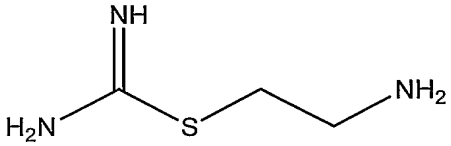
B18



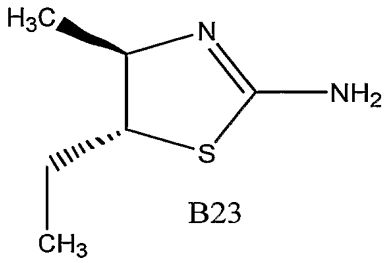
B19



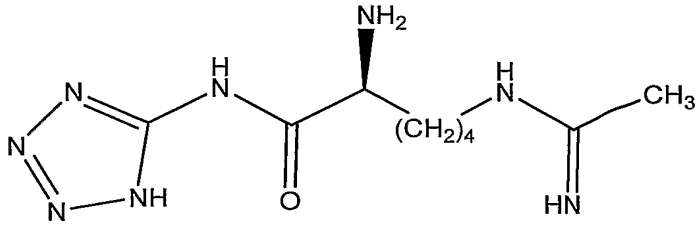
B20



B21

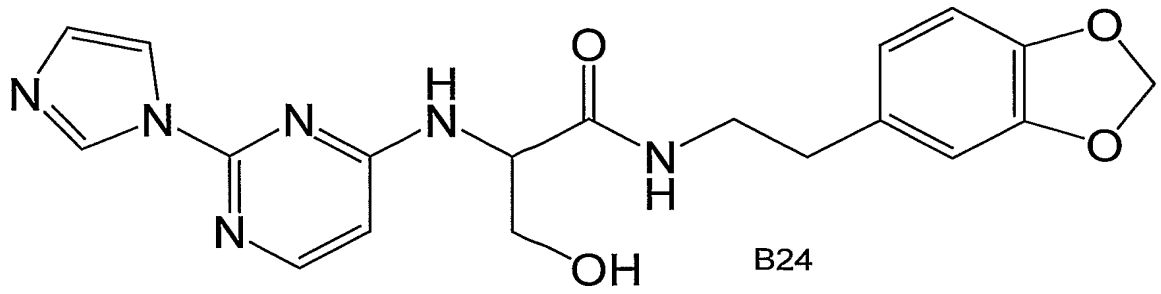


B23



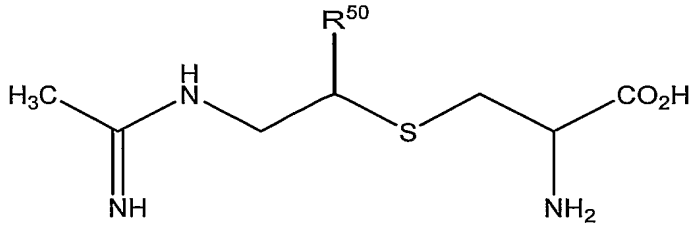
B22

One parent of the formula R^7OH is the iNOS-inhibitory alcohol B24 described in WO 98/37079 as example 53:

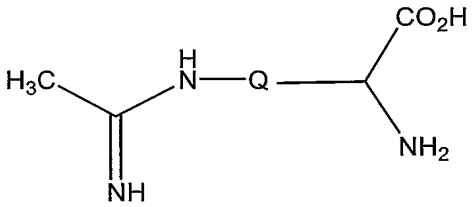


B24

Additionally, parents of the formulae R^4COOH and R^6NH_2 are chosen from the iNOS inhibitors described in US pat 6,355,689:



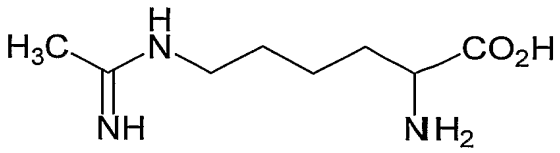
wherein R^{50} is chosen from C_1 to C_4 alkyl, C_3 to C_4 cycloalkyl, C_1 to C_4 hydroxyalkyl and C_1 to C_4 haloalkyl or US patent 5,863,931:



wherein Q is chosen from $-CH_2CH=CHCH_2-$, $-(CH_2)_pV(CH_2)_q-$, -O- , $-NR^{51}-$ and $-(CH_2)_rT(CH_2)_s-$; p is 2 or 3; q is 1 or 2; V is $S(O)_x$; x is 0, 1 or 2; R^{51} is H or C_{1-6} alkyl; r is 1 or 2; s is 1 or 2; and T is cyclobutyl, phenyl or pyridyl. Other iNOS inhibitors useful as parent structures in the instant invention may be found in US patents 6,451,821; 5,132,453; 5,830,917; 5,684,008; 6,207,708; 6,344,473; 6,143,790; 5,866,612; 6,369,272; 6,552,052; 6,495,544; 6,403,830; 5,629,322; 6,110,930; 6,228,866; 6,274,557; 6,432,947; 6,451,821; 5,449,688; 5,723,451; 5,854,251; 5,863,931; 5,889,056; 5,919,787; 5,945,408; 5,972,940; 5,981,511; 6,355,689; 6,423,705; 6,586,474 and 6,465,686; in US published applications 20030013702; 20020037927; 20020049202; 20030119826; 20020022631; 20020198243; 20030064978; 20030195256; 20030207896; 20030109522; 20040087653; in PCT applications WO99/62875; WO99/628785; WO01/78719; WO01/05748;

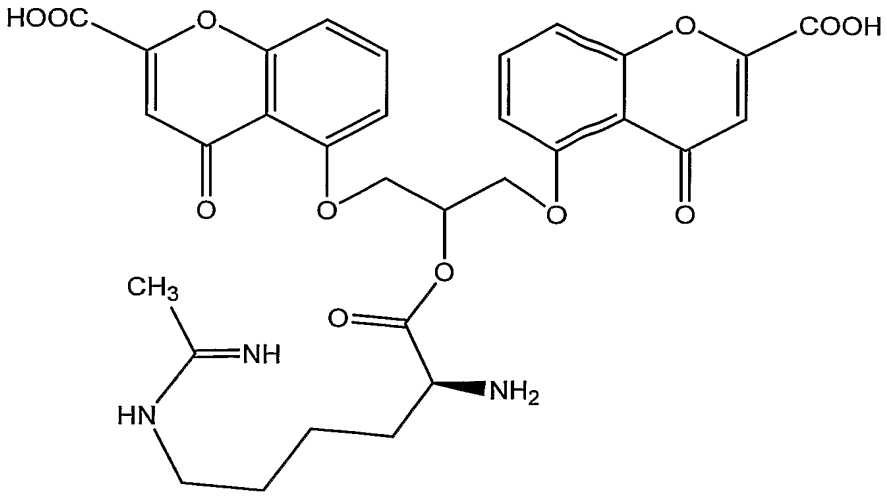
WO01/14371; WO96/35677; WO96/33175; WO96/15120; WO95/11014; WO95/11231; WO95/25717; WO95/24382; WO94/12165; WO94/14780; WO93/13055; WO02/076395; WO03/097163; WO03/097050; WO03/026638; WO00/13709; WO00/26195; WO00/61126; WO01/00195; WO01/58867; WO01/74351; WO01/94325; WO02/00648; WO02/50021; WO93/05775; WO95/13805; WO95/34534; WO96/15120; WO96/27593; WO98/02555; WO98/37079; WO99/26657; WO99/46240; WO04/012726; WO01/72703; WO95/24832; WO94/12165; WO94/14780; WO04/106312 and WO03/026668 and in European published applications EP0446699; EP1299365; EP765308; EP957087 and EP1282413. As indicated in paragraph [0041] below, the relevant disclosures of all are incorporated herein by reference.

[0017] The concept of "parent", as used herein, refers to a compound, such as **B1**



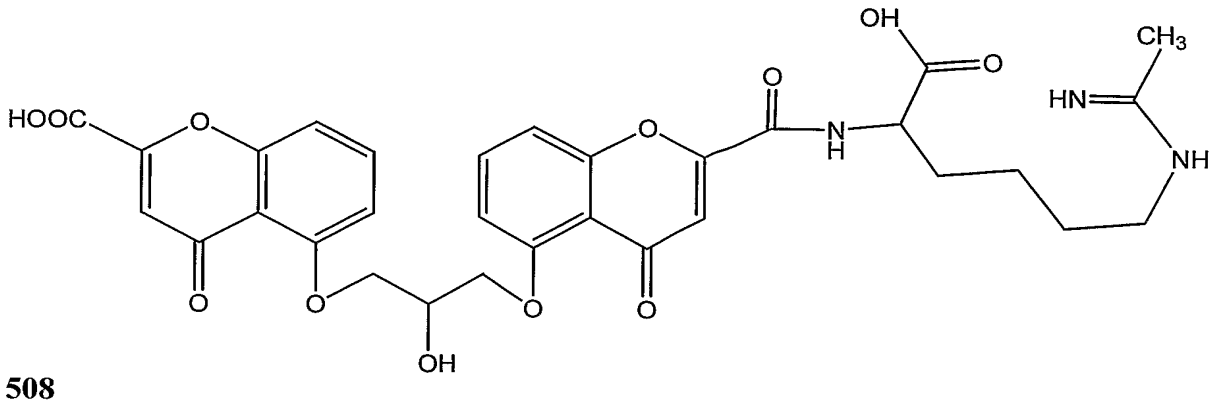
B1

which is a selective inhibitor of iNOS. When the residue of this parent is attached to a chroman of formula I, one possible resulting structure is **512**:



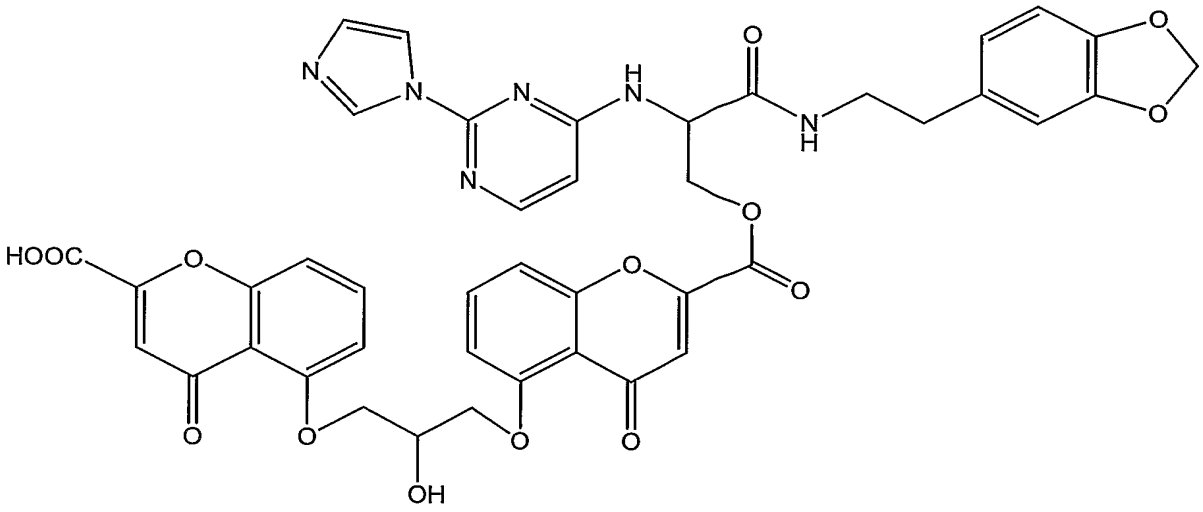
512

in which R^3 is -(C=O)R^4 and -(C=O)R^4 is the deshydroxy residue of a carboxylic acid, the parent of which, **B1**, is an inhibitor of iNOS. It will be immediately apparent that **B1** could also be attached to **I** as an amide:

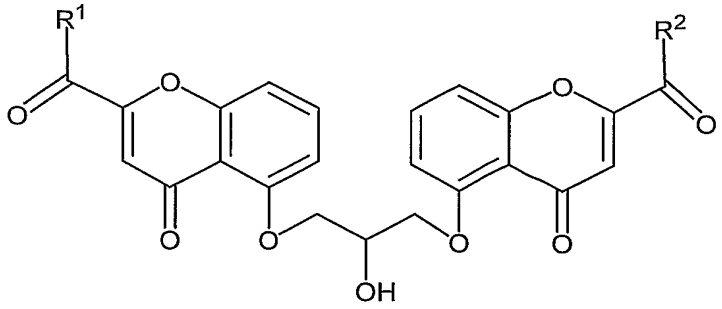


508

in which case R^2 is -NHR^6 and -NHR^6 is the deshydrogen residue of an amine, the parent of which, **B1**, is an inhibitor of iNOS. Similarly, alcohols may be attached as esters:



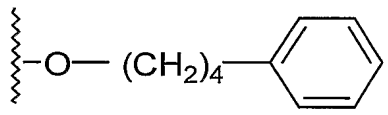
[0018] In one subgenus, R^1 and R^2 are chosen from hydroxy, C_1, C_2, C_3, C_4, C_5, and C_6 straight and branched alkoxy, -R^5, -NHR^6, -OR^7 and -O^-X^+; and R^3 is chosen from hydrogen, -(C=O)R^4, -(C=O)R^5, -(C=O)NHR^6 and -(C=O)OR^7. Another genus includes compounds of formula:



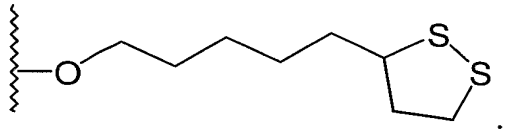
in which R^1 is chosen from -G-O(C=O)R^4, -NHR^6 and OR^7 ; and R^2 is chosen from hydroxy, C_1, C_2, C_3, C_4, C_5, and C_6 straight and branched alkoxy, R^5 and $-O^- X$.

[0019] In another subgenus at least one of R^1, R^2 and R^3 is -G-O(C=O)R^4 or -(C=O)-G-O(C=O)R^4; and G is chosen from -OCH_2- and -$OCH(CH_3)$-. "G" in these cases forms an acetal of formaldehyde or acetaldehyde with the oxygen of -O(C=O)R^4. Acetals are particularly suitable as linkers that are readily cleaved under physiological conditions.

[0020] R^5 substituents include straight or branched alkyl groups of 1, 2, 3, 4, 5 and 6 carbon atoms, PBO and DTP:

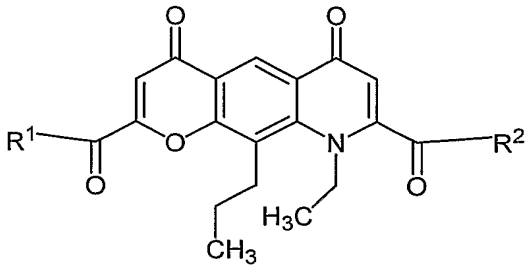


and



PBO DTP

In other subgenera the compounds are dioxo-4H,6H-pyrano[3,2-g]quinolines

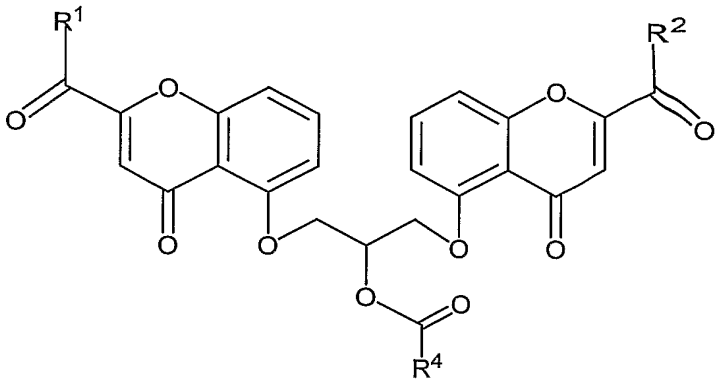


II

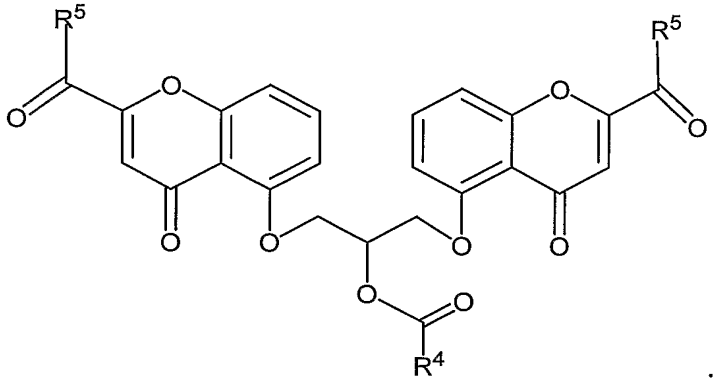
wherein R^1 is chosen from hydroxy, R^5 and $-O^- X$; and R^2 is chosen from -G-O(C=O)R^4, -NHR^6 and OR^7 or wherein R^1 is chosen from -G-O(C=O)R^4, -NHR^6 and OR^7 ; and

R^2 is chosen from hydroxy, R^5 and $-O^- X$.

[0021] Other subgenera include esters of formula



wherein R^1 and R^2 are chosen from hydroxy, C_1, C_2, C_3, C_4, C_5, and C_6 straight and branched alkoxy and $-O^- X^+$; and esters of formula



[0022] The compounds described herein may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. Each chiral center may be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present invention is meant to include all such possible isomers, as well as, their racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

[0023] The graphic representations of racemic, ambiscalemic and scalemic or enantiomerically pure compounds used herein are taken from Maehr J. Chem. Ed. 62, 114-120 (1985): solid and broken wedges are used to denote the absolute configuration of a chiral element; wavy lines and single thin lines indicate disavowal of any stereochemical implication which the bond it represents could generate; solid and broken bold lines are geometric descriptors indicating the relative configuration shown but denoting racemic character; and wedge outlines and dotted or broken lines denote enantiomerically pure compounds of indeterminate absolute configuration.

[0024] The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and, unless a specific configuration is expressly indicated, the depiction is not intended to designate a particular configuration; thus a carbon-carbon double bond depicted arbitrarily herein as *E* may be *Z*, *E*, or a mixture of the two in any proportion.

[0025] As used herein, and as would be understood by the person of skill in the art, the recitation of "a compound" is intended to include salts and solvates of that compound.

[0026] The term "solvate" refers to a compound in the solid state, wherein molecules of a suitable solvent are incorporated in the crystal lattice. A suitable solvent for therapeutic administration is physiologically tolerable at the dosage administered. Examples of suitable solvents for therapeutic administration are ethanol and water. When water is the solvent, the solvate is referred to as a hydrate. In general, solvates are formed by dissolving the compound in the appropriate solvent and isolating the solvate by cooling or using an antisolvent. The solvate is typically dried or azeotroped under ambient conditions.

[0027] Compounds of formula I may contain basic or acidic residues, allowing them to be presented as salts. The term "pharmaceutically acceptable salt" refers to salts whose counter ion (anion) derives from pharmaceutically acceptable non-toxic acids

and bases. When the compounds contain a quat or a basic residue, suitable pharmaceutically acceptable base addition salts for the compounds of the present invention include inorganic acids, organic acids and, in the case of quats, water (which formally furnishes the hydroxide anion). Examples include hydroxide, acetate, benzenesulfonate (besylate), benzoate, bicarbonate, bisulfate, carbonate, camphorsulfonate, citrate, ethanesulfonate, fumarate, gluconate, glutamate, glycolate, bromide, chloride, isethionate, lactate, maleate, malate, mandelate, methanesulfonate, mucate, nitrate, pamoate, pantothenate, phosphate, succinate, sulfate, tartrate, trifluoroacetate, p-toluenesulfonate, acetamidobenzoate, adipate, alginate, aminosalicylate, anhydromethylenecitrate, ascorbate, aspartate, calcium edetate, camphorate, camsylate, caprate, caproate, caprylate, cinnamate, cyclamate, dichloroacetate, edetate (EDTA), edisylate, embonate, estolate, esylate, fluoride, formate, gentisate, gluceptate, glucuronate, glycerophosphate, glycolate, glycollylarsanilate, hexylresorcinate, hippurate, hydroxynaphthoate, iodide, lactobionate, malonate, mesylate, napadisylate, napsylate, nicotinate, oleate, orotate, oxalate, oxoglutarate, palmitate, pectinate, pectinate polymer, phenylethylbarbiturate, picrate, pidolate, propionate, rhodanide, salicylate, sebacate, stearate, tannate, theoclate, tosylate, and the like. When the compounds contain an acidic residue, suitable pharmaceutically acceptable base addition salts for the compounds of the present invention include ammonium, metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Other base addition salts includes those made from: arecoline, arginine, barium, benethamine, benzathine, betaine, bismuth, clemizole, copper, deanol, diethylamine, diethylaminoethanol, epolamine, ethylenediamine, ferric, ferrous, glucamine, glucosamine, histidine, hydrabamine, imidazole, isopropylamine, manganic, manganous, methylglucamine, morpholine, morpholineethanol, N-ethylmorpholine, N-ethylpiperidine, piperazine, piperidine, polyamine resins, purines, theobromine, triethylamine, trimethylamine, tripropylamine, trolamine, and tromethamine.

Definitions

[0028] Throughout this specification the terms and substituents retain their definitions.

[0029] Alkyl is intended to include linear, branched, or cyclic hydrocarbon structures and combinations thereof. When not otherwise restricted, the term refers to alkyl of 20 or fewer carbons. Lower alkyl refers to alkyl groups of 1, 2, 3, 4, 5 and 6 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s-and t-butyl and the like. Methyl is preferred. Preferred alkyl and alkylene groups are those of C_{20} or below (e.g. C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}). Cycloalkyl is a subset of alkyl and includes cyclic hydrocarbon groups of 3, 4, 5, 6, 7, and 8 carbon atoms. Examples of cycloalkyl groups include c-propyl, c-butyl, c-pentyl, norbornyl, adamantyl and the like.

[0030] C_1 to C_{20} Hydrocarbon includes alkyl, cycloalkyl, alkenyl, alkynyl, aryl and combinations thereof. Examples include benzyl, phenethyl, cyclohexylmethyl, camphoryl and naphthylethyl.

[0031] Alkoxy or alkoxyl refers to groups of 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of a straight, branched, cyclic configuration and combinations thereof attached to the parent structure through an oxygen. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like. Lower-alkoxy refers to groups containing one to four carbons.

[0032] Oxaalkyl refers to alkyl residues in which one or more carbons (and their associated hydrogens) have been replaced by oxygen. Examples include methoxypropoxy, 3,6,9-trioxadecyl and the like. The term oxaalkyl is intended as it is understood in the art [see Naming and Indexing of Chemical Substances for Chemical Abstracts, published by the American Chemical Society, ¶196, but without the restriction of ¶127(a)], i.e. it refers to compounds in which the oxygen is bonded via a

single bond to its adjacent atoms (forming ether bonds). Similarly, thiaalkyl and azaalkyl refer to alkyl residues in which one or more carbons have been replaced by sulfur or nitrogen, respectively. Examples include ethylaminoethyl and methylthiopropyl.

[0033] Acyl refers to groups of 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of a straight, branched, cyclic configuration, saturated, unsaturated and aromatic and combinations thereof, attached to the parent structure through a carbonyl functionality. One or more carbons in the acyl residue may be replaced by nitrogen, oxygen or sulfur as long as the point of attachment to the parent remains at the carbonyl. Examples include formyl, acetyl, propionyl, isobutyryl, *t*-butoxycarbonyl, benzoyl, benzyloxycarbonyl and the like. Lower-acyl refers to groups containing one to four carbons.

[0034] Aryl and heteroaryl mean a 5- or 6-membered aromatic or heteroaromatic ring containing 0-3 heteroatoms selected from O, N, or S; a bicyclic 9- or 10-membered aromatic or heteroaromatic ring system containing 0-3 heteroatoms selected from O, N, or S; or a tricyclic 13- or 14-membered aromatic or heteroaromatic ring system containing 0-3 heteroatoms selected from O, N, or S. Aromatic 6- to 14-membered carbocyclic rings include, *e.g.,* benzene, naphthalene, indane, tetralin, and fluorene and the 5- to 10-membered aromatic heterocyclic rings include, *e.g.*, imidazole, pyridine, indole, thiophene, benzopyranone, thiazole, furan, benzimidazole, quinoline, isoquinoline, quinoxaline, pyrimidine, pyrazine, tetrazole and pyrazole.

[0035] Arylalkyl means an alkyl residue attached to an aryl ring. Examples are benzyl, phenethyl and the like.

[0036] Substituted alkyl, aryl, cycloalkyl, heterocyclyl etc. refer to alkyl, aryl, cycloalkyl, or heterocyclyl wherein up to three H atoms in each residue are replaced with halogen, haloalkyl, hydroxy, loweralkoxy, carboxy, carboalkoxy (also referred to as alkoxycarbonyl), carboxamido (also referred to as alkylaminocarbonyl), cyano, carbonyl, nitro, amino, alkylamino, dialkylamino, mercapto, alkylthio, sulfoxide,

sulfone, acylamino, amidino, phenyl, benzyl, heteroaryl, phenoxy, benzyloxy, or heteroaryloxy.

[0037] The term "halogen" means fluorine, chlorine, bromine or iodine.

[0038] A "quaternary ammonium salt" as used herein refers to a substituent of the general formula - $N^+R^7R^8R^9$ X^-, in which R^7 is C_1 to C_{20} hydrocarbon or forms a five- to seven-membered ring with R^8; R^8 is alkyl or forms a five- to seven-membered ring with R^7; R^9 is alkyl or together with R^7 or R^8 forms a second five- to seven-membered ring; and X is an anion.

[0039] The term "prodrug" refers to a compound that is made more active *in vivo*. Commonly the conversion of prodrug to drug occurs by enzymatic processes in the liver or blood of the mammal. Many of the compounds of the invention may be chemically modified without absorption into the systemic circulation, and in those cases, activation *in vivo* may come about by chemical action (as in the acid-catalyzed cleavage of the acetals "G") or through the intermediacy of enzymes in the respiratory system, for example by esterases within the alveoli.

[0040] The terms "methods of treating or preventing" mean amelioration, prevention or relief from the symptoms and/or effects associated with lipid disorders. The term "preventing" as used herein refers to administering a medicament beforehand to forestall or obtund an acute episode. The person of ordinary skill in the medical art (to which the present method claims are directed) recognizes that the term "prevent" is not an absolute term. In the medical art it is understood to refer to the prophylactic administration of a drug to substantially diminish the likelihood or seriousness of a condition, and this is the sense intended in applicants' claims. As used herein, reference to "treatment" of a patient is intended to include prophylaxis.

[0041] Throughout this application, various references are referred to. The disclosures of these publications in their entireties are hereby incorporated by reference as if written herein.

[0001] The term "mammal" is used in its dictionary sense. The term "mammal" includes, for example, mice, hamsters, rats, cows, sheep, pigs, goats, and horses, monkeys, dogs (e.g., *Canis familiaris*), cats, rabbits, guinea pigs, and primates, including humans. Humans would be the preferred subjects of the methods of treatment.

[0042] Terminology related to "protecting", "deprotecting" and "protected" functionalities occurs throughout this application. Such terminology is well understood by persons of skill in the art and is used in the context of processes which involve sequential treatment with a series of reagents. In that context, a protecting group refers to a group which is used to mask a functionality during a process step in which it would otherwise react, but in which reaction is undesirable. The protecting group prevents reaction at that step, but may be subsequently removed to expose the original functionality. The removal or "deprotection" occurs after the completion of the reaction or reactions in which the functionality would interfere. Thus, when a sequence of reagents is specified, as it is in the processes of the invention, the person of ordinary skill can readily envision those groups that would be suitable as "protecting groups". Suitable groups for that purpose are discussed in standard textbooks in the field of chemistry, such as Protective Groups in Organic Synthesis by T.W.Greene [John Wiley & Sons, New York, 1991].

[0043] The abbreviations Me, Et, Ph, Tf, Ts and Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, toluenesulfonyl and methanesulfonyl respectively. For example, in the tables, OEt refers to ethoxy. A comprehensive list of abbreviations utilized by organic chemists (i.e. persons of ordinary skill in the art) appears in the first issue of each volume of the Journal of Organic Chemistry. The list, which is typically presented in a table entitled "Standard List of Abbreviations" is incorporated herein by reference.

[0044] The invention also encompasses pharmaceutical compositions comprising a pharmaceutically acceptable carrier and the foregoing compounds. One embodiment

of the invention includes aerosol pharmaceutical compositions. Another embodiment of the invention includes oral formulations including tablets, capsules and syrups.

[0045] While it may be possible for the compounds to be administered as the raw chemical, it is preferable to present them as a pharmaceutical composition. According to a further aspect, the present invention provides a pharmaceutical composition comprising a compound as described above, or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0046] The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), rectal and topical (including dermal, buccal, sublingual and intraocular) administration. The most suitable route may depend upon the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

[0047] Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

[0048] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or

granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the active ingredient therein.

[0049] The pharmaceutical compositions may include a "pharmaceutically acceptable inert carrier", and this expression is intended to include one or more inert excipients, which include starches, polyols, granulating agents, microcrystalline cellulose, diluents, lubricants, binders, disintegrating agents, and the like. If desired, tablet dosages of the disclosed compositions may be coated by standard aqueous or nonaqueous techniques, "Pharmaceutically acceptable carrier" also encompasses controlled release means.

[0050] Compositions of the present invention may also optionally include other therapeutic ingredients, anti-caking agents, preservatives, sweetening agents, colorants, flavors, desiccants, plasticizers, dyes, and the like. Any such optional ingredient must, of course, be compatible with the compound of the invention to insure the stability of the formulation.

[0051] The agents, alone or in combination with other suitable components, can be administered by pulmonary route utilizing several techniques including but not limited to intratracheal instillation (delivery of solution into the lungs by syringe), intratracheal delivery of liposomes, insufflation (administration of powder formulation by syringe or any other similar device into the lungs) and aerosol inhalation. Formulations suitable for pulmonary route inhalation include sterile solutions for nebulization comprising a therapeutically effective amount of the compound dissolved in aqueous saline solution and optionally containing a preservative such as benzalkonium chloride or chlorobutanol, and aerosol formulations comprising a therapeutically effective amount dissolved or suspended in an appropriate propellant. Aerosols (e.g., jet or ultrasonic nebulizers, metered-dose inhalers (MDIs), and dry-powder inhalers (DPIs)) can also be used in intranasal

applications. Aerosols may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy. Aerosol formulations are stable dispersions or suspensions of solid material and liquid droplets in a gaseous medium and can be placed into pressurized acceptable propellants, such as hydrofluroalkanes (HFAs, i.e. HFA-134a and HFA-227, or a mixture thereof), dichlorodifluoromethane (or other chlorofluocarbon propellants such as a mixture of Propellants 11, 12, and/or 114), propane, nitrogen, and the like. Pulmonary formulations may include permeation enhancers such as fatty acids, and saccharides, chelating agents, enzyme inhibitors (e.g., protease inhibitors), adjuvants (e.g., glycocholate, surfactin, span 85, and nafamostat), preservatives (e.g., benzalkonium chloride or chlorobutanol), and ethanol (normally up to 5% but possibly up to 20%, by weight). Ethanol is commonly included in aerosol compositions as it can improve the function of the metering valve and in some cases also improve the stability of the dispersion. Pulmonary formulations may also include surfactants, which include but are not limited to bile salts and those described in U.S. 6,524,557 and references therein. The surfactants described in U.S. 6,524,557, e.g., a C8-C16 fatty acid salt, a bile salt, a phospholipid, or alkyl saccharide are advantageous in that some of them also reportedly enhance absorption of the compound in the formulation.

[0052] Also suitable in the invention are dry powder formulations comprising a therapeutically effective amount of active compound blended with an appropriate carrier and adapted for use in connection with a dry-powder inhaler. Absorption enhancers which can be added to dry powder formulations of the present invention include those described in U.S. 6,632,456. WO 02/080884 describes new methods for the surface modification of powders. Aerosol formulations may include U.S. 5,230,884, U.S. 5,292,499, WO 017/8694, WO 01/78696, U.S. 2003019437, U. S. 20030165436, and WO 96/40089 (which includes vegetable oil). Sustained release formulations suitable for inhalation are described in U.S. 20010036481A1, 20030232019A1, and U.S. 20040018243A1 as well as in WO 01/13891, WO 02/067902, WO 03/072080, and WO 03/079885. Pulmonary formulations containing microparticles are described in WO 03/015750, U.S. 20030008013, and WO 00/00176. Pulmonary formulations containing stable glassy state powder are

described in U.S. 20020141945 and U.S. 6,309,671. Other aerosol formulations are described in EP 1338272A1 WO 90/09781, U. S. 5,348,730, U.S. 6,436,367, WO 91/04011, and U.S. 6,294,153 and U.S. 6,290,987 describes a liposomal based formulation that can be administered via aerosol or other means. Powder formulations for inhalation are described in U.S. 20030053960 and WO 01/60341. The agents can be administered intranasally as described in U.S. 20010038824.

[0053] While the pulmonary route is advantageous in most instances, there may also be instances in which other routes of administration may be advantageous. For example, oral administration may be desirable. In that regard, one may contemplate administration using a formulation in which the compound is releasably encapsulated by modified amino acids, as described in US patent 5,811,127. One may also contemplate administration as an implantable sustained-release dosage form, such as described in US published application 20040115236.

[0054] The dose range for adult humans is generally from 0.005 mg to 10 g/day orally. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors, including the age and sex of the patient, the precise disorder being treated, and its severity.

[0055] The invention also relates to methods for preventing and/or treating pulmonary disorders. According to the invention one may administer a compound as described above for treating bronchospasm, for inducing bronchodilation, for treating chronic obstructive pulmonary disease (including chronic bronchitis with normal airflow), for treating asthma (including allergen-induced asthma, viral-induced asthma, cold-induced asthma, pollution-induced asthma and exercise-induced asthma) and for treating rhinitis (including allergic rhinitis).

[0056] A broad spectrum of respiratory diseases and disorders have been recognized, many of which have overlapping and interacting etiologies. One of the most widespread and prevalent of these diseases in western populations is the chronic disease referred to as "asthma". Other such disorders are also characterized by acute pulmonary vasoconstriction such as may result from pneumonia, traumatic injury, aspiration or inhalation injury, fat embolism in the lung, acidosis inflammation of the lung, adult respiratory distress syndrome, acute pulmonary edema, acute mountain sickness, post-cardiac surgery, acute pulmonary hypertension, persistent pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, herapin-protamine reactions, sepsis, status asthmaticus or hypoxia (including iatrogenic hypoxia) and other forms of reversible pulmonary vasoconstriction. Such pulmonary disorders also are also characterized by inflammation of the lung including those associated with the migration into the lung of nonresident cell types including the various leucocyte subclasses. Also included in the respiratory disorders contemplated are: bullous disease, pigeon fancier's disease, asthmatic bronchitis, chronic bronchitis with airway obstruction (chronic obstructive bronchitis), emphysema, farmer's lung, allergic eye diseases (including allergic conjunctivitis, vernal conjunctivitis, vernal keratoconjunctivitis, and giant papillary conjunctivitis), and cystic fibrosis and other diseases which are characterized by inflammation of the lung and/or excess mucosal secretion. Other physiological events which are contemplated to be controlled include platelet activation in the lung.

[0057] The methods for treating pulmonary disorders also encompass co-administering a mast-cell stabilizer and an iNOS inhibitor in the form of a salt, in which one of the mast-cell stabilizer and the iNOS inhibitor is a cation or dication, and the other is an anion or dianion.

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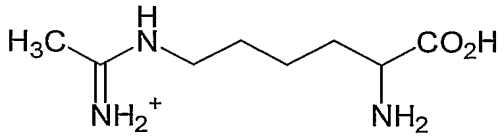

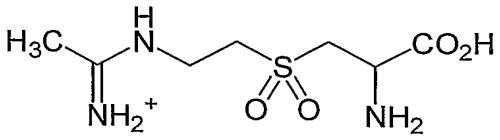

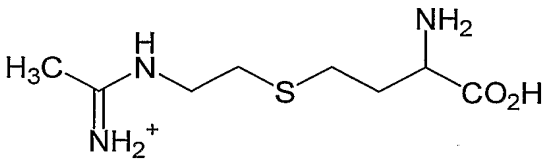

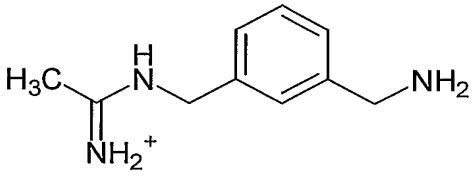

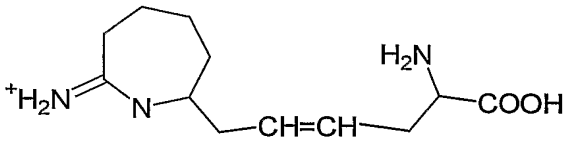

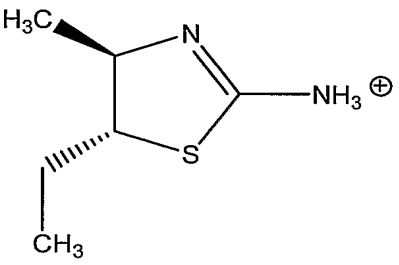

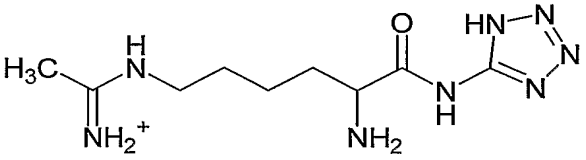

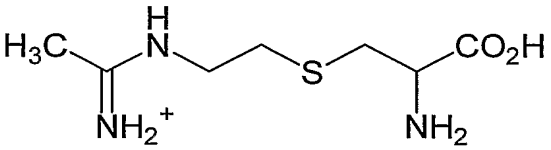

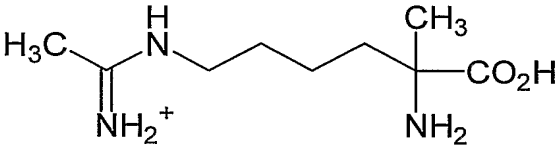

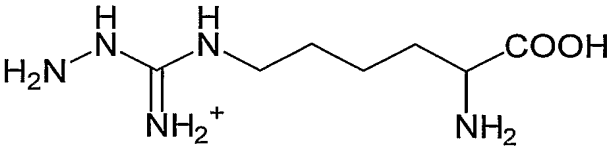

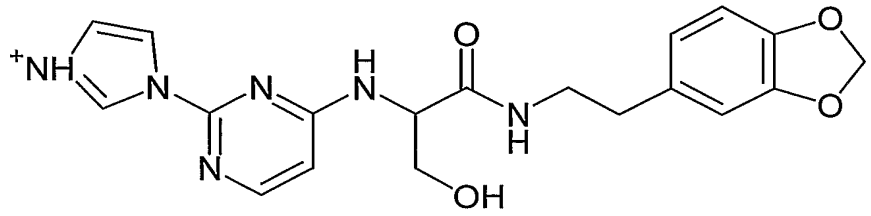

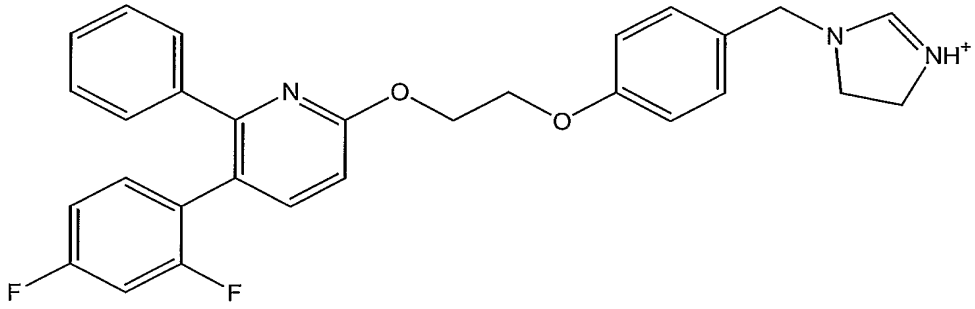

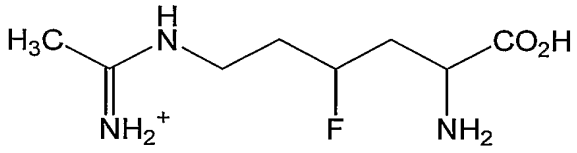

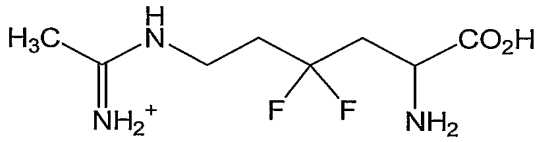

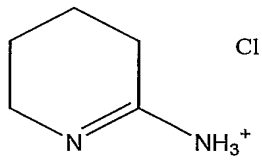

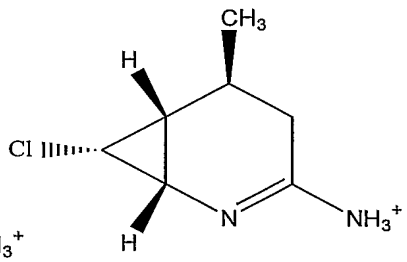

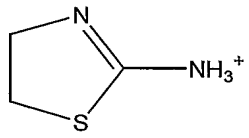

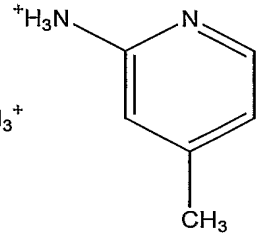

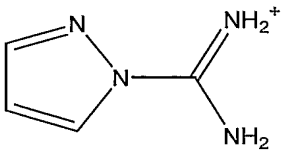

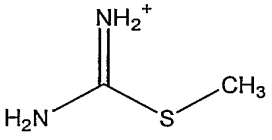

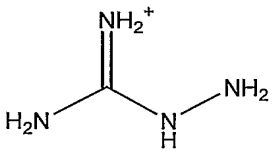

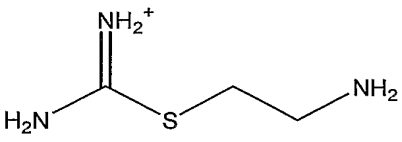

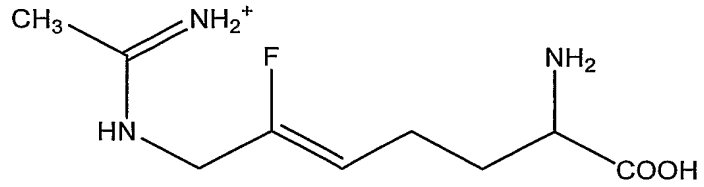

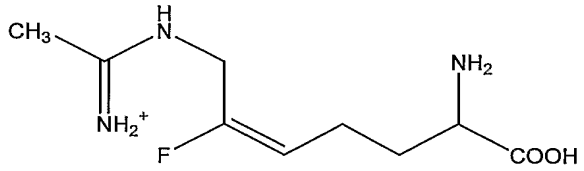

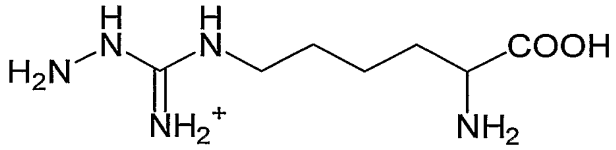

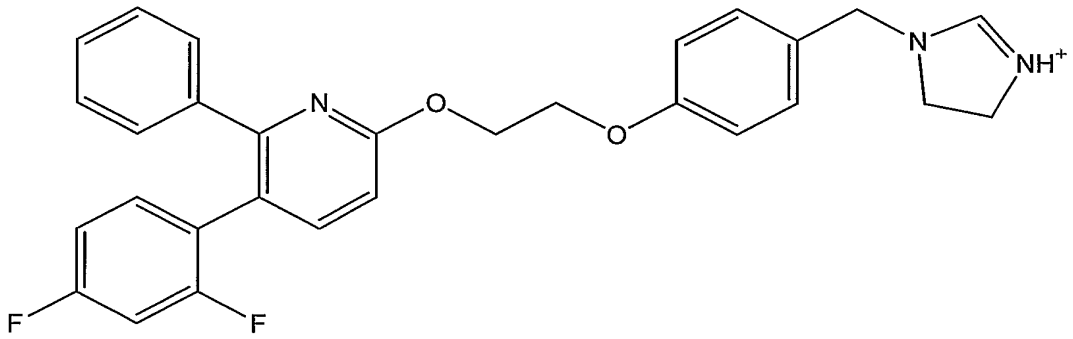

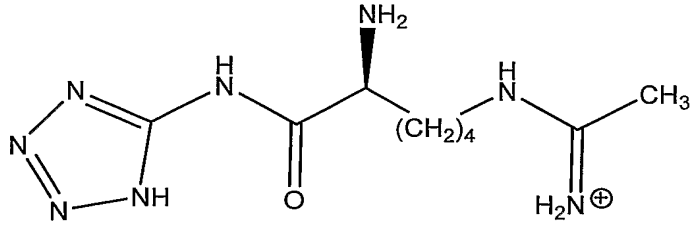

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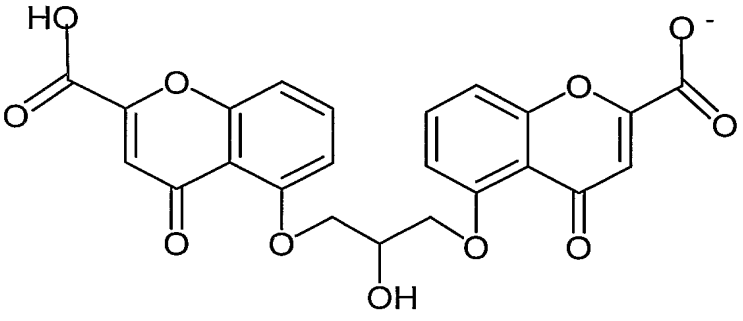
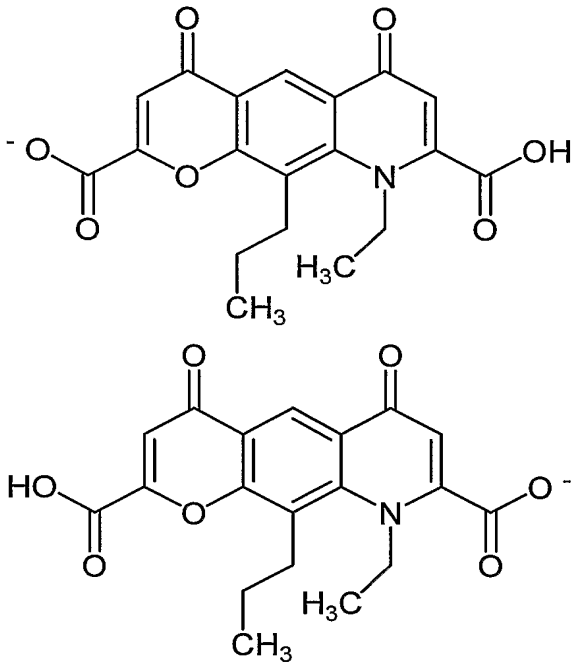




and their corresponding dianions.

The invention also encompasses the salts themselves.

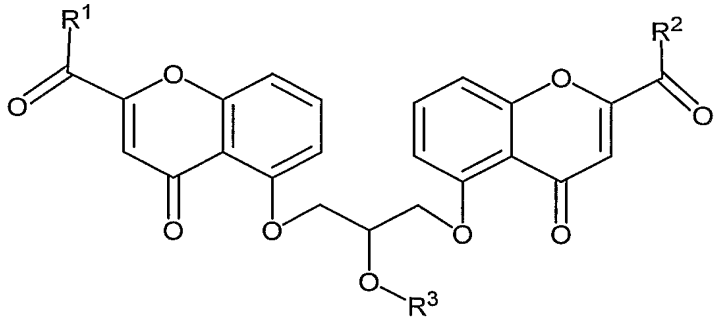
[0058] Combination therapy can be achieved by administering two or more agents, each of which is formulated and administered separately, or by administering two or more agents in a single formulation. Other combinations are also encompassed by combination therapy. For example, two agents can be formulated together and administered in conjunction with a separate formulation containing a third agent. While the two or more agents in the combination therapy can be administered simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by minutes, hours, days, or weeks. Thus, the two or more agents can be administered within minutes of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks of each other. In some cases even longer intervals are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so. Combination therapy can also include two or more

administrations of one or more of the agents used in the combination. For example, if agent X and agent Y are used in a combination, one could administer them sequentially in any combination one or more times, e.g., in the order X-Y-X, X-X-Y, Y-X-Y, Y-Y-X, X-X-Y-Y, etc.

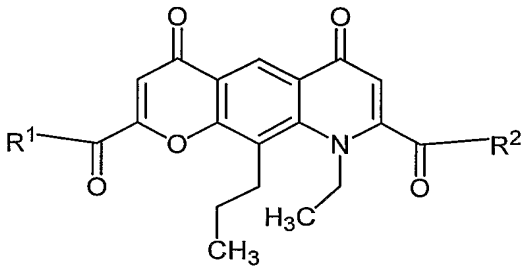
[0059] The compounds of the present invention can be coadministered with any of the following: (1) β-agonists including but not limited to: albuterol (Proventil®, Salbutamol®, Ventolin®), bambuterol, bitoterol, clenbuterol, fenoterol, formoterol, isoetharine (Bronkosol®, Bronkometer®), metaproterenol (Alupent®, Metaprel®), pirbuterol (Maxair®), reproterol, rimiterol, salmeterol, terbutaline (Brethaire®, Brethine®, Bricanyl®), adrenalin, isoproterenol (Isuprel®), epinephrine bitartrate (Primatene®), ephedrine, orciprenline, fenoterol and isoetharine; (2) steroids, including but not limited to beclomethasone, beclomethasone dipropionate, betamethasone, budesonide, bunedoside, butixocort, dexamethasone, flunisolide, fluocortin, fluticasone, hydrocortisone, methyl prednisone, mometasone, predonisolone, predonisone, tipredane, tixocortal, triamcinolone, and triamcinolone acetonide; (3) β2-agonist-corticosteroid combinations [e.g., salmeterol-fluticasone (Advair®), formoterol-budesonid (Symbicort®)]; (4) leukotriene D4 receptor antagonists/leukotriene antagonists/LTD4 antagonists (i.e., any compound that is capable of blocking, inhibiting, reducing or otherwise interrupting the interaction between leukotrienes and the Cys LTI receptor) including but not limited to: zafirlukast, montelukast, montelukast sodium (Singulair®), pranlukast, iralukast, pobilukast, SKB-106,203 and compounds described as having LTD4 antagonizing activity described in US 5,565,473; (5) 5-lipoxygenase inhibitors and/or leukotriene biosynthesis inhibitors [e.g. zileuton and BAY1005 (CA registry 128253-31-6)]; (6) histamine H1 receptor antagonists/antihistamines (i.e. any compound that is capable of blocking, inhibiting, reducing or otherwise interrupting the interaction between histamine and its receptor) including but not limited to: astemizole, acrivastine, antazoline, azatadine, azelastine, astamizole, bromopheniramine, bromopheniramine maleate, carbinoxamine, carebastine, cetirizine, chlorpheniramine, chloropheniramine maleate, cimetidine ,clemastine, cyclizine, cyproheptadine, descarboethoxyloratadine, dexchlorpheniramine, dimethindene, diphenhydramine, diphenylpyraline, doxylamine

succinate, doxylarnine, ebastine, efletirizine, epinastine, farnotidine, fexofenadine, hydroxyzine, hydroxyzine, ketotifen, levocabastine, levocetirizine, levocetirizine, loratadine, meclizine, mepyramine, mequitazine, methdilazine, mianserin, mizolastine, noberastine, norasternizole, noraztemizole, phenindamine, pheniramine, picumast, promethazine, pynlamine, pyrilamine, ranitidine, temelastine, terfenadine, trimeprazine, tripelenamine, and triprolidine; (7) an anticholinergic including but not limited to: atropine, benztropine, biperiden, flutropium, hyoscyamine, ilutropium, ipratropium, ipratropium bromide, methscopolamine, oxybutinin, rispenzepine, scopolamine, and tiotropium; (8) an anti-tussive including but not limited to: dextromethorphan, codeine, and hydromorphone; (9) a decongestant including but not limited to: pseudoephedrine and phenylpropanolamine; (10) an expectorant including but not limited to: guafenesin, guaicolsulfate, terpin, ammonium chloride, glycerol guaicolate, and iodinated glycerol; (11) a bronchodilator including but not limited to: theophylline and aminophylline; (12) an anti-inflammatory including but not limited to: fluribiprofen, diclophenac, indomethacin, ketoprofen, S-ketroprophen, tenoxicam; (13) a PDE inhibitor including but not limited to filaminast, denbufyllene piclamilast, roflumilast, zardaverine, and rolipram; (14) a recombinant humanized monoclonal antibody [e.g. xolair (also called omalizumab), rhuMab, and talizumab]; and (14) a humanized lung surfactant [e.g. Surfaxin®, formerly known as dsc-104 (Discovery Laboratories)].

[0060] Finally one may describe the compounds of formula I or II



I



II

in means-plus-function terms. In other words, -O(C=O)R^4 is the deshydrogen residue of a carboxylic acid, the parent of which, R^4COOH, is a chemical means for inhibiting inducible nitric oxide synthase (iNOS);

-(C=O)R^4 is the deshydroxy residue of a carboxylic acid, the parent of which, R^4COOH, is a chemical means for inhibiting iNOS;

-NHR^6 is the deshydrogen residue of an amine, the parent of which, R^6NH_2, is a chemical means for inhibiting iNOS;

-OR^7 is the deshydrogen residue of an alcohol, the parent of which, R^7OH, is a chemical means for inhibiting iNOS.

Chemical means for inhibiting iNOS are compounds (i.e. chemicals) that exhibit IC_{50} below 25 μM when tested against human iNOS according to the method of Moore *et al.* J. Med. Chem. 39, 669-672 (1996). Examples of many such compounds are shown above as **B1** through **B24**. In one embodiment, inhibitors are those with IC_{50} below 10 μM. In another embodiment, inhibitors are those with an IC_{50} below 5 μM. For the purpose of the invention, iNOS inhibitors should be selective for iNOS over eNOS and nNOS. Selective means having an IC_{50} against iNOS that is no more than $1/10^{th}$ the IC_{50} against nNOS and eNOS as measured by the method described in Moore (*op. cit.*) Unless some other meaning is clear from its context, the term "iNOS inhibitor", not further modified, as used herein refers to a selective iNOS inhibitor.

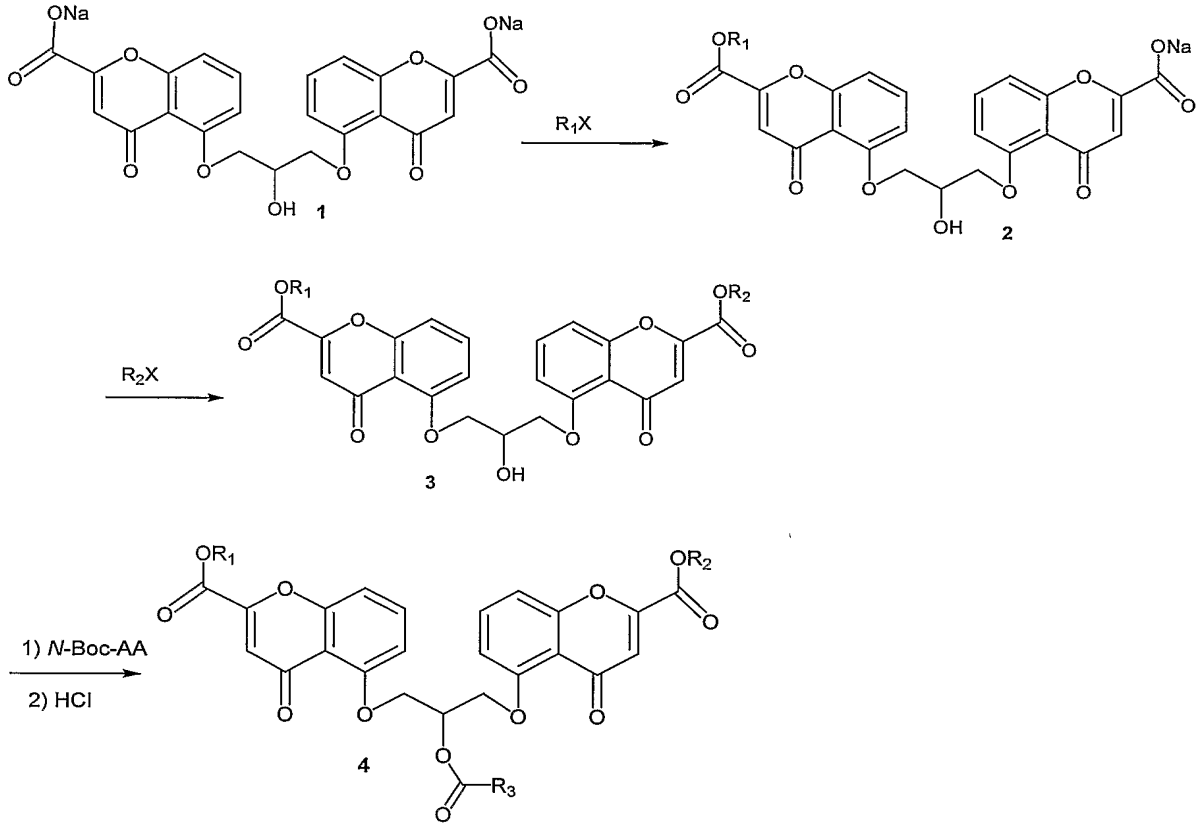
[0061] The compounds of the present invention may possess one or more of the following advantages: they lessen bronchial epithelial damage in asthma; they exhibit improved stability, formulation and manufacturing characteristics; they possess improved pharmacokinetic properties, allowing in many cases, once or twice daily inhaled dosing; they offer an alternative to steroid therapy

[0062] The efficacy of the compounds of the invention may be demonstrated in a test that measures airway hyperresponsiveness [see Muijsers *et al.* Br. J. Pharmacol. 134, 434 (2001); Elwood *et al.* Am.Rev.Respir.Dis. 145, 1289-1294 (1992) and Eynott *et al.* Eur. J. Pharm. 452, 123 (2002)] or in a test that measures inflammation in an airway [see Chen *et al.* Acta Pharmacol. Sin. 24, 697 (2003)]. The activity of the compounds of the invention can be tested in the presence or absence of serum. In the presence of serum, one would expect both iNOS activity and mast cell stabilization activity, which can be assayed in methods described by Misko *et al.* [Eur.J.Pharmacol. 233, 119-125 (1993)] and Kusner *et al.* [J.Pharmacol.Exp.Ther. 184, 41-46 (1973)] respectively.

[0063] In general, the compounds of the present invention may be prepared by the methods illustrated in the general reaction schemes as, for example, described below, or by modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants that are in themselves known, but are not mentioned here.

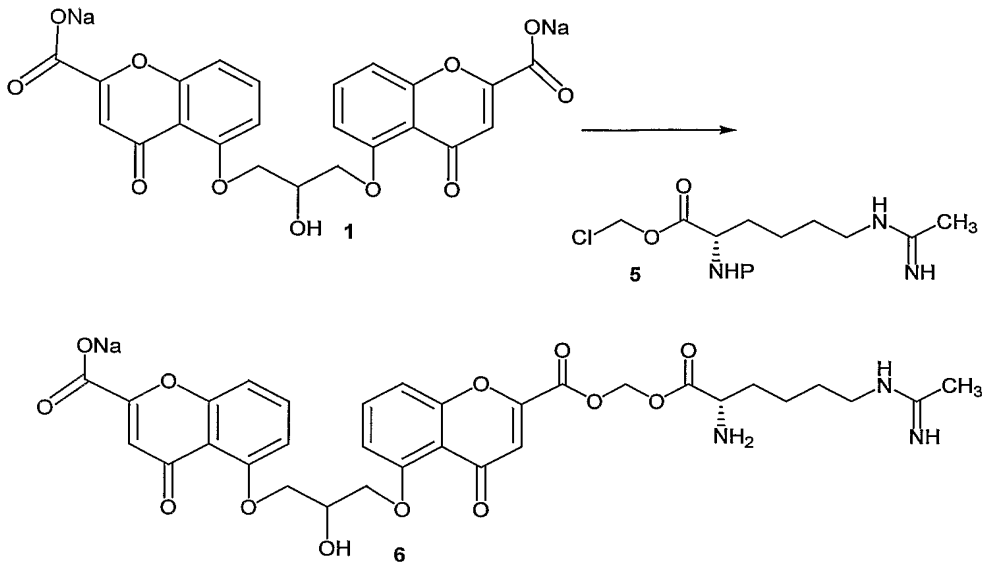
[0064] In Scheme I disodium chromylglycate **1** is treated with one equivalent of an alkyl halide in a dipolar aprotic solvent such as dimethylformamide (DMF) to provide the corresponding mono-ester **2**. Typically, this procedure also produces some diester **3**, wherein R1=R2 and unreacted **1**. After separation of the mono-ester **2** it can be converted into diester **3** by reaction with an alkyl halide in a dipolar aprotic solvent to provide the diester **3**. The diester **3** is then condensed with an appropriately protected acid, such as an N-Boc-amino acid inhibitor of iNOS, in the presence of a dehydrating agent, such as 1,3-dicyclohexylcarbodiimide (DCC), to provide the protected ester. The protecting group is then removed to provide the desired chromyl iNOS inhibitors **4**. In the case of an N-Boc-amino acid, the protecting group can be removed by an acid such as HCl in dioxane.

Scheme I



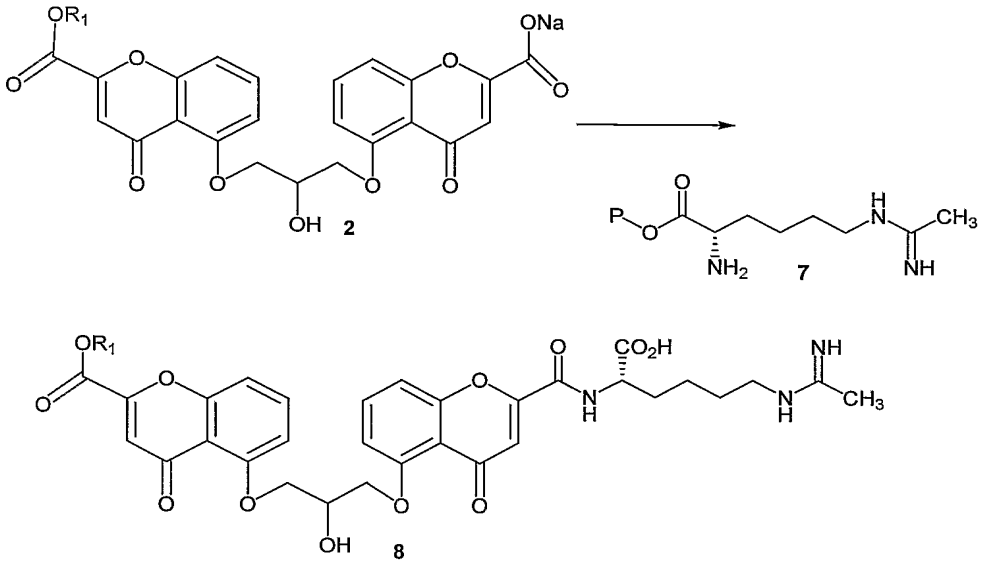
[0065] In Scheme II disodium chromylglycate **1** is treated with one equivalent the chloromethyl ester of a protected iNOS inhibitor such as **5** to provide, after purification, the corresponding ester. The ester is then deprotected to afford the desired chromyl iNOS inhibitor **6**.

Scheme II



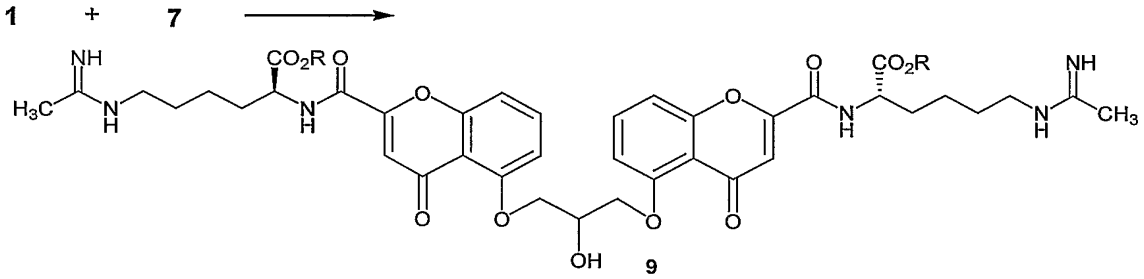
[0066] Scheme III illustrates the method for the preparation of mono-ester amide derivatives **8**. The route commences with the coupling of an orthogonally protected ester of an iNOS inhibitor **7** with the mono-ester **2** in the presence of a amide coupling agent such as 1,3-dicyclohexylcarbodiimide. The resulting amide derivative is then converted into the desired analogues **8** by removal of the ester of the iNOS moiety. The ester moiety of the iNOS inhibitor can be such things as the tert-butyl ester, the beta-trimethylsilylethyl ester, para-methoxybenzyl ester, and the like. If the iNOS inhibitor component does not possess an acid substituent then the amine can be coupled directly to **2** without the need for protection and deprotection. If the desired product is the free acid of **8** (R^1=H) the route can be to saponify the ester of **8**, or to couple one equivalent of the protected iNOS inhibitor **7** with **1** followed by removal of the protecting groups.

Scheme III

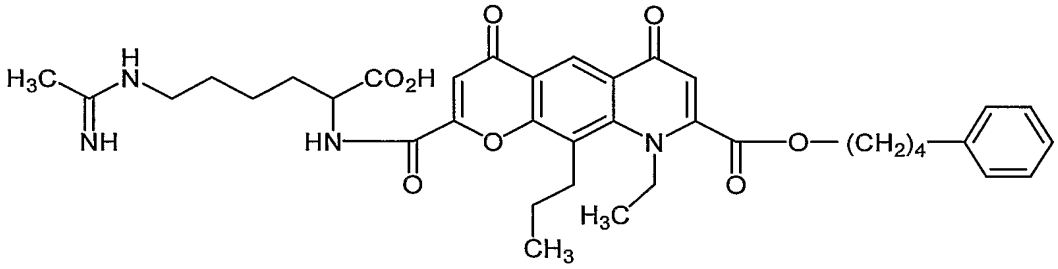


[0067] Illustrated in Scheme IV is the method used for the preparation of bis-iNOS amides of chromyln. The method involves coupling of **1** with the ester protected iNOS inhibitor moiety **7** in the presence of a dehydrating agent such as 1,3-dicyclohexylcarbodiimide to produce the ester protected version of **9**, R=ester. In a subsequent step the ester moiety is converted to the corresponding acid, **9**, R=H, by saponification. Suitable esters are those listed in Scheme III.

Scheme IV

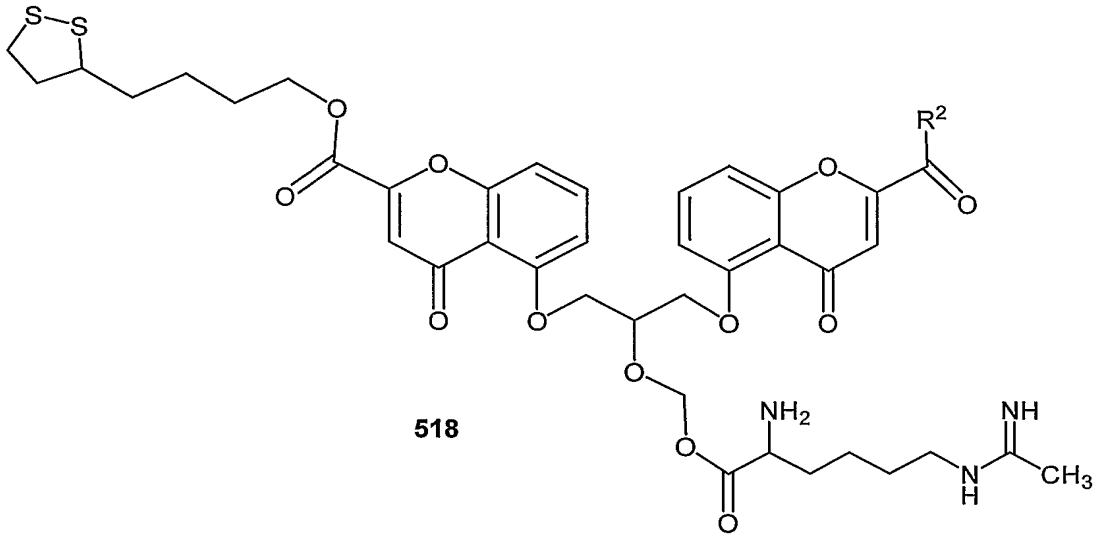


[0068] Compounds that are representative of the invention are shown in Tables 1 and 2 below. In these tables the numbers and abbreviations refer to structures presented above. Thus, for example, the compound of example **111** in Table 1 is described as an amide of B1 and an ester of PBO attached to the nedocromil core. The structure of the compound would be:



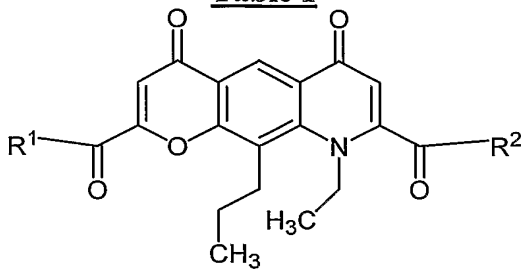
111

[0069] In all of the compounds in the tables, when an amide is formed, it is formed from the primary α-amine when R^1 or R^2 is an α-amino acid (B1-B3, B5, B7-B13), and from the primary amine or amidine in the other cases (B4, B6, B14-B19, B22, B23). When the residue is B20, the point of attachment is on the terminal nitrogen of the hydrazine; when the residue is B21, the point of attachment is the primary amine. The entry "acetal" in the columns headed "linkage" refer to acetals of formaldehyde, i.e. $-OCH_2O-$. Thus the compound of example **518** in Table 2 has the structure:



518

Table 1



Example #	R1	linkage	R2	linkage
100	B1	ester	-OH	n/a
101	B1	ester	-OEt	ester
102	B1	ester	DTP	ester
103	B1	ester	PBO	ester
104	B1	acetal	-OH	n/a
105	B1	acetal	-OEt	ester
106	B1	acetal	DTP	ester
107	B1	acetal	PBO	ester
108	B1	amide	-OH	n/a
109	B1	amide	-OEt	ester
110	B1	amide	DTP	ester
111	B1	amide	PBO	ester
112	-OH	n/a	B1	ester
113	-OEt	ester	B1	ester
114	DTP	ester	B1	ester
115	PBO	ester	B1	ester
116	-OH	n/a	B1	acetal
117	-OEt	ester	B1	acetal
118	DTP	ester	B1	acetal
119	PBO	ester	B1	acetal
120	-OH	n/a	B1	amide
121	-OEt	ester	B1	amide
122	DTP	ester	B1	amide
123	PBO	ester	B1	amide
124	B2	ester	-OH	n/a
125	B2	ester	-OEt	ester
126	B2	ester	DTP	ester
127	B2	ester	PBO	ester
128	B2	acetal	-OH	n/a
129	B2	acetal	-OEt	ester
130	B2	acetal	DTP	ester
131	B2	acetal	PBO	ester
132	B2	amide	-OH	n/a
133	B2	amide	-OEt	ester

Example #	R1	linkage	R2	linkage
134	B2	amide	DTP	ester
135	B2	amide	PBO	ester
136	-OH	n/a	B2	ester
137	-OEt	ester	B2	ester
138	DTP	ester	B2	ester
139	PBO	ester	B2	ester
140	-OH	n/a	B2	acetal
141	-OEt	ester	B2	acetal
142	DTP	ester	B2	acetal
143	PBO	ester	B2	acetal
144	-OH	n/a	B2	amide
145	-OEt	ester	B2	amide
146	DTP	ester	B2	amide
147	PBO	ester	B2	amide
148	B3	ester	-OH	n/a
149	B3	ester	-OEt	ester
150	B3	ester	DTP	ester
151	B3	ester	PBO	ester
152	B3	acetal	-OH	n/a
153	B3	acetal	-OEt	ester
154	B3	acetal	DTP	ester
155	B3	acetal	PBO	ester
156	B3	amide	-OH	n/a
157	B3	amide	-OEt	ester
158	B3	amide	DTP	ester
159	B3	amide	PBO	ester
160	-OH	n/a	B3	ester
161	-OEt	ester	B3	ester
162	DTP	ester	B3	ester
163	PBO	ester	B3	ester
164	-OH	n/a	B3	acetal
165	-OEt	ester	B3	acetal
166	DTP	ester	B3	acetal
167	PBO	ester	B3	acetal
168	-OH	n/a	B3	amide
169	-OEt	ester	B3	amide
170	DTP	ester	B3	amide
171	PBO	ester	B3	amide
172	B4	amide	-OH	n/a
173	B4	amide	-OEt	ester
174	B4	amide	DTP	ester
175	B4	amide	PBO	ester
176	-OH	n/a	B4	amide
177	-OEt	ester	B4	amide
178	DTP	ester	B4	amide

Example #	R1	linkage	R2	linkage
179	PBO	ester	B4	amide
180	B5	ester	-OH	n/a
181	B5	ester	-OEt	ester
182	B5	ester	DTP	ester
183	B5	ester	PBO	ester
184	B5	acetal	-OH	n/a
185	B5	acetal	-OEt	ester
186	B5	acetal	DTP	ester
187	B5	acetal	PBO	ester
188	B5	amide	-OH	n/a
189	B5	amide	-OEt	ester
190	B5	amide	DTP	ester
191	B5	amide	PBO	ester
192	-OH	n/a	B5	ester
193	-OEt	ester	B5	ester
194	DTP	ester	B5	ester
195	PBO	ester	B5	ester
196	-OH	n/a	B5	acetal
197	-OEt	ester	B5	acetal
198	DTP	ester	B5	acetal
199	PBO	ester	B5	acetal
200	-OH	n/a	B5	amide
201	-OEt	ester	B5	amide
202	DTP	ester	B5	amide
203	PBO	ester	B5	amide
204	B6	amide	-OH	n/a
205	B6	amide	-OEt	ester
206	B6	amide	DTP	ester
207	B6	amide	PBO	ester
208	-OH	n/a	B6	amide
209	-OEt	ester	B6	amide
210	DTP	ester	B6	amide
211	PBO	ester	B6	amide
212	B7	ester	-OH	n/a
213	B7	ester	-OEt	ester
214	B7	ester	DTP	ester
215	B7	ester	PBO	ester
216	B7	acetal	-OH	n/a
217	B7	acetal	-OEt	ester
218	B7	acetal	DTP	ester
219	B7	acetal	PBO	ester
220	B7	amide	-OH	n/a
221	B7	amide	-OEt	ester
222	B7	amide	DTP	ester
223	B7	amide	PBO	ester

Example #	R1	linkage	R2	linkage
224	-OH	n/a	B7	ester
225	-OEt	ester	B7	ester
226	DTP	ester	B7	ester
227	PBO	ester	B7	ester
228	-OH	n/a	B7	acetal
229	-OEt	ester	B7	acetal
230	DTP	ester	B7	acetal
231	PBO	ester	B7	acetal
232	-OH	n/a	B7	amide
233	-OEt	ester	B7	amide
234	DTP	ester	B7	amide
235	PBO	ester	B7	amide
236	B8	ester	-OH	n/a
237	B8	ester	-OEt	ester
238	B8	ester	DTP	ester
239	B8	ester	PBO	ester
240	B8	acetal	-OH	n/a
241	B8	acetal	-OEt	ester
242	B8	acetal	DTP	ester
243	B8	acetal	PBO	ester
244	B8	amide	-OH	n/a
245	B8	amide	-OEt	ester
246	B8	amide	DTP	ester
247	B8	amide	PBO	ester
248	-OH	n/a	B8	ester
249	-OEt	ester	B8	ester
250	DTP	ester	B8	ester
251	PBO	ester	B8	ester
252	-OH	n/a	B8	acetal
253	-OEt	ester	B8	acetal
254	DTP	ester	B8	acetal
255	PBO	ester	B8	acetal
256	-OH	n/a	B8	amide
257	-OEt	ester	B8	amide
258	DTP	ester	B8	amide
259	PBO	ester	B8	amide
260	B9	ester	-OH	n/a
261	B9	ester	-OEt	ester
262	B9	ester	DTP	ester
263	B9	ester	PBO	ester
264	B9	acetal	-OH	n/a
265	B9	acetal	-OEt	ester
266	B9	acetal	DTP	ester
267	B9	acetal	PBO	ester
268	B9	amide	-OH	n/a

Example #	R1	linkage	R2	linkage
269	B9	amide	-OEt	ester
270	B9	amide	DTP	ester
271	B9	amide	PBO	ester
272	-OH	n/a	B9	ester
273	-OEt	ester	B9	ester
274	DTP	ester	B9	ester
275	PBO	ester	B9	ester
276	-OH	n/a	B9	acetal
277	-OEt	ester	B9	acetal
278	DTP	ester	B9	acetal
279	PBO	ester	B9	acetal
280	-OH	n/a	B9	amide
281	-OEt	ester	B9	amide
282	DTP	ester	B9	amide
283	PBO	ester	B9	amide
284	B10	ester	-OH	n/a
285	B10	ester	-OEt	ester
286	B10	ester	DTP	ester
287	B10	ester	PBO	ester
288	B10	acetal	-OH	n/a
289	B10	acetal	-OEt	ester
290	B10	acetal	DTP	ester
291	B10	acetal	PBO	ester
292	B10	amide	-OH	n/a
293	B10	amide	-OEt	ester
294	B10	amide	DTP	ester
295	B10	amide	PBO	ester
296	-OH	n/a	B10	ester
297	-OEt	ester	B10	ester
298	DTP	ester	B10	ester
299	PBO	ester	B10	ester
300	-OH	n/a	B10	acetal
301	-OEt	ester	B10	acetal
302	DTP	ester	B10	acetal
303	PBO	ester	B10	acetal
304	-OH	n/a	B10	amide
305	-OEt	ester	B10	amide
306	DTP	ester	B10	amide
307	PBO	ester	B10	amide
308	B11	ester	-OH	n/a
309	B11	ester	-OEt	ester
310	B11	ester	DTP	ester
311	B11	ester	PBO	ester
312	B11	acetal	-OH	n/a
313	B11	acetal	-OEt	ester

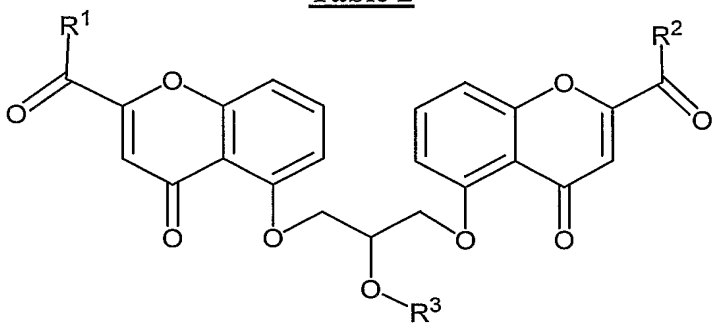
Example #	R1	linkage	R2	linkage
314	B11	acetal	DTP	ester
315	B11	acetal	PBO	ester
316	B11	amide	-OH	n/a
317	B11	amide	-OEt	ester
318	B11	amide	DTP	ester
319	B11	amide	PBO	ester
320	-OH	n/a	B11	ester
321	-OEt	ester	B11	ester
322	DTP	ester	B11	ester
323	PBO	ester	B11	ester
324	-OH	n/a	B11	acetal
325	-OEt	ester	B11	acetal
326	DTP	ester	B11	acetal
327	PBO	ester	B11	acetal
328	-OH	n/a	B11	amide
329	-OEt	ester	B11	amide
330	DTP	ester	B11	amide
331	PBO	ester	B11	amide
332	B12	ester	-OH	n/a
333	B12	ester	-OEt	ester
334	B12	ester	DTP	ester
335	B12	ester	PBO	ester
336	B12	acetal	-OH	n/a
337	B12	acetal	-OEt	ester
338	B12	acetal	DTP	ester
339	B12	acetal	PBO	ester
340	B12	amide	-OH	n/a
341	B12	amide	-OEt	ester
342	B12	amide	DTP	ester
343	B12	amide	PBO	ester
344	-OH	n/a	B12	ester
345	-OEt	ester	B12	ester
346	DTP	ester	B12	ester
347	PBO	ester	B12	ester
348	-OH	n/a	B12	acetal
349	-OEt	ester	B12	acetal
350	DTP	ester	B12	acetal
351	PBO	ester	B12	acetal
352	-OH	n/a	B12	amide
353	-OEt	ester	B12	amide
354	DTP	ester	B12	amide
355	PBO	ester	B12	amide
356	B13	ester	-OH	n/a
357	B13	ester	-OEt	ester
358	B13	ester	DTP	ester

Example #	R1	linkage	R2	linkage
359	B13	ester	PBO	ester
360	B13	acetal	-OH	n/a
361	B13	acetal	-OEt	ester
362	B13	acetal	DTP	ester
363	B13	acetal	PBO	ester
364	B13	amide	-OH	n/a
365	B13	amide	-OEt	ester
366	B13	amide	DTP	ester
367	B13	amide	PBO	ester
368	-OH	n/a	B13	ester
369	-OEt	ester	B13	ester
370	DTP	ester	B13	ester
371	PBO	ester	B13	ester
372	-OH	n/a	B13	acetal
373	-OEt	ester	B13	acetal
374	DTP	ester	B13	acetal
375	PBO	ester	B13	acetal
376	-OH	n/a	B13	amide
377	-OEt	ester	B13	amide
378	DTP	ester	B13	amide
379	PBO	ester	B13	amide
380	B14	amide	-OH	n/a
381	B14	amide	-OEt	ester
382	B14	amide	DTP	ester
383	B14	amide	PBO	ester
384	-OH	n/a	B14	amide
385	-OEt	ester	B14	amide
386	DTP	ester	B14	amide
387	PBO	ester	B14	amide
388	B15	amide	-OH	n/a
389	B15	amide	-OEt	ester
390	B15	amide	DTP	ester
391	B15	amide	PBO	ester
392	-OH	n/a	B15	amide
393	-OEt	ester	B15	amide
394	DTP	ester	B15	amide
395	PBO	ester	B15	amide
396	B16	amide	-OH	n/a
397	B16	amide	-OEt	ester
398	B16	amide	DTP	ester
399	B16	amide	PBO	ester
400	-OH	n/a	B16	amide
401	-OEt	ester	B16	amide
402	DTP	ester	B16	amide
403	PBO	ester	B16	amide

Example #	R1	linkage	R2	linkage
404	B17	amide	-OH	n/a
405	B17	amide	-OEt	ester
406	B17	amide	DTP	ester
407	B17	amide	PBO	ester
408	-OH	n/a	B17	amide
409	-OEt	ester	B17	amide
410	DTP	ester	B17	amide
411	PBO	ester	B17	amide
412	B18	amide	-OH	n/a
413	B18	amide	-OEt	ester
414	B18	amide	DTP	ester
415	B18	amide	PBO	ester
416	-OH	n/a	B18	amide
417	-OEt	ester	B18	amide
418	DTP	ester	B18	amide
419	PBO	ester	B18	amide
420	B19	amide	-OH	n/a
421	B19	amide	-OEt	ester
422	B19	amide	DTP	ester
423	B19	amide	PBO	ester
424	-OH	n/a	B19	amide
425	-OEt	ester	B19	amide
426	DTP	ester	B19	amide
427	PBO	ester	B19	amide
428	B20	amide	-OH	n/a
429	B20	amide	-OEt	ester
430	B20	amide	DTP	ester
431	B20	amide	PBO	ester
432	-OH	n/a	B20	amide
433	-OEt	ester	B20	amide
434	DTP	ester	B20	amide
435	PBO	ester	B20	amide
436	B21	amide	-OH	n/a
437	B21	amide	-OEt	ester
438	B21	amide	DTP	ester
439	B21	amide	PBO	ester
440	-OH	n/a	B21	amide
441	-OEt	ester	B21	amide
442	DTP	ester	B21	amide
443	PBO	ester	B21	amide
444	B22	amide	-OH	n/a
445	B22	amide	-OEt	ester
446	B22	amide	DTP	ester
447	B22	amide	PBO	ester
448	-OH	n/a	B22	amide

Example #	R1	linkage	R2	linkage
449	-OEt	ester	B22	amide
450	DTP	ester	B22	amide
451	PBO	ester	B22	amide
452	B23	amide	-OH	n/a
453	B23	amide	-OEt	ester
454	B23	amide	DTP	ester
455	B23	amide	PBO	ester
456	-OH	n/a	B23	amide
457	-OEt	ester	B23	amide
458	DTP	ester	B23	amide
459	PBO	ester	B23	amide
460	B24	ester	-OH	n/a
461	B24	ester	-OEt	ester
462	B24	ester	DTP	ester
463	B24	ester	PBO	ester
464	-OH	n/a	B24	ester
465	-OEt	ester	B24	ester
466	DTP	ester	B24	ester
467	PBO	ester	B24	ester

Table 2



Example #	R1	linkage	R2	linkage	R3	linkage
500	B1	ester	-OH	n/a	-H	n/a
501	B1	ester	-OEt	ester	-H	n/a
502	B1	ester	DTP	ester	-H	n/a
503	B1	ester	PBO	ester	-H	n/a
504	B1	acetal	-OH	n/a	-H	n/a
505	B1	acetal	-OEt	ester	-H	n/a
506	B1	acetal	DTP	ester	-H	n/a
507	B1	acetal	PBO	ester	-H	n/a
508	B1	amide	-OH	n/a	-H	n/a
509	B1	amide	-OEt	ester	-H	n/a
510	B1	amide	DTP	ester	-H	n/a

Example #	R1	linkage	R2	linkage	R3	linkage
511	B1	amide	PBO	ester	-H	n/a
512	-OH	n/a	-OH	n/a	B1	ester
513	-OEt	ester	-OH	n/a	B1	ester
514	DTP	ester	-OH	n/a	B1	ester
515	PBO	ester	-OH	n/a	B1	ester
516	-OH	n/a	-OH	n/a	B1	acetal
517	-OEt	ester	-OH	n/a	B1	acetal
518	DTP	ester	-OH	n/a	B1	acetal
519	PBO	ester	-OH	n/a	B1	acetal
520	B2	ester	-OH	n/a	-H	n/a
521	B2	ester	-OEt	ester	-H	n/a
522	B2	ester	DTP	ester	-H	n/a
523	B2	ester	PBO	ester	-H	n/a
524	B2	acetal	-OH	n/a	-H	n/a
525	B2	acetal	-OEt	ester	-H	n/a
526	B2	acetal	DTP	ester	-H	n/a
527	B2	acetal	PBO	ester	-H	n/a
528	B2	amide	-OH	n/a	-H	n/a
529	B2	amide	-OEt	ester	-H	n/a
530	B2	amide	DTP	ester	-H	n/a
531	B2	amide	PBO	ester	-H	n/a
532	-OH	n/a	-OH	n/a	B2	ester
533	-OEt	ester	-OH	n/a	B2	ester
534	DTP	ester	-OH	n/a	B2	ester
535	PBO	ester	-OH	n/a	B2	ester
536	-OH	n/a	-OH	n/a	B2	acetal
537	-OEt	ester	-OH	n/a	B2	acetal
538	DTP	ester	-OH	n/a	B2	acetal
539	PBO	ester	-OH	n/a	B2	acetal
540	B3	ester	-OH	n/a	-H	n/a
541	B3	ester	-OEt	ester	-H	n/a
542	B3	ester	DTP	ester	-H	n/a
543	B3	ester	PBO	ester	-H	n/a
544	B3	acetal	-OH	n/a	-H	n/a
545	B3	acetal	-OEt	ester	-H	n/a
546	B3	acetal	DTP	ester	-H	n/a
547	B3	acetal	PBO	ester	-H	n/a
548	B3	amide	-OH	n/a	-H	n/a
549	B3	amide	-OEt	ester	-H	n/a
550	B3	amide	DTP	ester	-H	n/a
551	B3	amide	PBO	ester	-H	n/a
552	-OH	n/a	-OH	n/a	B3	ester
553	-OEt	ester	-OH	n/a	B3	ester
554	DTP	ester	-OH	n/a	B3	ester
555	PBO	ester	-OH	n/a	B3	ester
556	-OH	n/a	-OH	n/a	B3	acetal
557	-OEt	ester	-OH	n/a	B3	acetal
558	DTP	ester	-OH	n/a	B3	acetal

Example #	R1	linkage	R2	linkage	R3	linkage
559	PBO	ester	-OH	n/a	B3	acetal
560	B4	amide	-OH	n/a	-H	n/a
561	B4	amide	-OEt	ester	-H	n/a
562	B4	amide	DTP	ester	-H	n/a
563	B4	amide	PBO	ester	-H	n/a
564	B5	ester	-OH	n/a	-H	n/a
565	B5	ester	-OEt	ester	-H	n/a
566	B5	ester	DTP	ester	-H	n/a
567	B5	ester	PBO	ester	-H	n/a
568	B5	acetal	-OH	n/a	-H	n/a
569	B5	acetal	-OEt	ester	-H	n/a
570	B5	acetal	DTP	ester	-H	n/a
571	B5	acetal	PBO	ester	-H	n/a
572	B5	amide	-OH	n/a	-H	n/a
573	B5	amide	-OEt	ester	-H	n/a
574	B5	amide	DTP	ester	-H	n/a
575	B5	amide	PBO	ester	-H	n/a
576	-OH	n/a	-OH	n/a	B5	ester
577	-OEt	ester	-OH	n/a	B5	ester
578	DTP	ester	-OH	n/a	B5	ester
579	PBO	ester	-OH	n/a	B5	ester
580	-OH	n/a	-OH	n/a	B5	acetal
581	-OEt	ester	-OH	n/a	B5	acetal
582	DTP	ester	-OH	n/a	B5	acetal
583	PBO	ester	-OH	n/a	B5	acetal
584	B6	amide	-OH	n/a	-H	n/a
585	B6	amide	-OEt	ester	-H	n/a
586	B6	amide	DTP	ester	-H	n/a
587	B6	amide	PBO	ester	-H	n/a
588	B7	ester	-OH	n/a	-H	n/a
589	B7	ester	-OEt	ester	-H	n/a
590	B7	ester	DTP	ester	-H	n/a
591	B7	ester	PBO	ester	-H	n/a
592	B7	acetal	-OH	n/a	-H	n/a
593	B7	acetal	-OEt	ester	-H	n/a
594	B7	acetal	DTP	ester	-H	n/a
595	B7	acetal	PBO	ester	-H	n/a
596	B7	amide	-OH	n/a	-H	n/a
597	B7	amide	-OEt	ester	-H	n/a
598	B7	amide	DTP	ester	-H	n/a
599	B7	amide	PBO	ester	-H	n/a
600	-OH	n/a	-OH	n/a	B7	ester
601	-OEt	ester	-OH	n/a	B7	ester
602	DTP	ester	-OH	n/a	B7	ester
603	PBO	ester	-OH	n/a	B7	ester
604	-OH	n/a	-OH	n/a	B7	acetal
605	-OEt	ester	-OH	n/a	B7	acetal
606	DTP	ester	-OH	n/a	B7	acetal

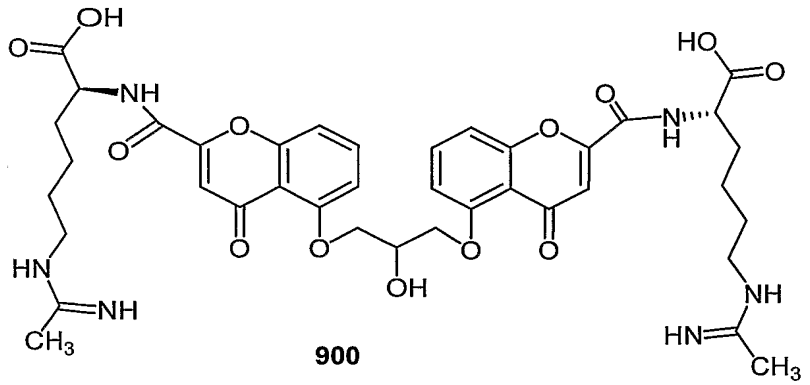
Example #	R1	linkage	R2	linkage	R3	linkage
607	PBO	ester	-OH	n/a	B7	acetal
608	B8	ester	-OH	n/a	-H	n/a
609	B8	ester	-OEt	ester	-H	n/a
610	B8	ester	DTP	ester	-H	n/a
611	B8	ester	PBO	ester	-H	n/a
612	B8	acetal	-OH	n/a	-H	n/a
613	B8	acetal	-OEt	ester	-H	n/a
614	B8	acetal	DTP	ester	-H	n/a
615	B8	acetal	PBO	ester	-H	n/a
616	B8	amide	-OH	n/a	-H	n/a
617	B8	amide	-OEt	ester	-H	n/a
618	B8	amide	DTP	ester	-H	n/a
619	B8	amide	PBO	ester	-H	n/a
620	-OH	n/a	-OH	n/a	B8	ester
621	-OEt	ester	-OH	n/a	B8	ester
622	DTP	ester	-OH	n/a	B8	ester
623	PBO	ester	-OH	n/a	B8	ester
624	-OH	n/a	-OH	n/a	B8	acetal
625	-OEt	ester	-OH	n/a	B8	acetal
626	DTP	ester	-OH	n/a	B8	acetal
627	PBO	ester	-OH	n/a	B8	acetal
628	B9	ester	-OH	n/a	-H	n/a
629	B9	ester	-OEt	ester	-H	n/a
630	B9	ester	DTP	ester	-H	n/a
631	B9	ester	PBO	ester	-H	n/a
632	B9	acetal	-OH	n/a	-H	n/a
633	B9	acetal	-OEt	ester	-H	n/a
634	B9	acetal	DTP	ester	-H	n/a
635	B9	acetal	PBO	ester	-H	n/a
636	B9	amide	-OH	n/a	-H	n/a
637	B9	amide	-OEt	ester	-H	n/a
638	B9	amide	DTP	ester	-H	n/a
639	B9	amide	PBO	ester	-H	n/a
640	-OH	n/a	-OH	n/a	B9	ester
641	-OEt	ester	-OH	n/a	B9	ester
642	DTP	ester	-OH	n/a	B9	ester
643	PBO	ester	-OH	n/a	B9	ester
644	-OH	n/a	-OH	n/a	B9	acetal
645	-OEt	ester	-OH	n/a	B9	acetal
646	DTP	ester	-OH	n/a	B9	acetal
647	PBO	ester	-OH	n/a	B9	acetal
648	B10	ester	-OH	n/a	-H	n/a
649	B10	ester	-OEt	ester	-H	n/a
650	B10	ester	DTP	ester	-H	n/a
651	B10	ester	PBO	ester	-H	n/a
652	B10	acetal	-OH	n/a	-H	n/a
653	B10	acetal	-OEt	ester	-H	n/a
654	B10	acetal	DTP	ester	-H	n/a

Example #	R1	linkage	R2	linkage	R3	linkage
655	B10	acetal	PBO	ester	-H	n/a
656	B10	amide	-OH	n/a	-H	n/a
657	B10	amide	-OEt	ester	-H	n/a
658	B10	amide	DTP	ester	-H	n/a
659	B10	amide	PBO	ester	-H	n/a
660	-OH	n/a	-OH	n/a	B10	ester
661	-OEt	ester	-OH	n/a	B10	ester
662	DTP	ester	-OH	n/a	B10	ester
663	PBO	ester	-OH	n/a	B10	ester
664	-OH	n/a	-OH	n/a	B10	acetal
665	-OEt	ester	-OH	n/a	B10	acetal
666	DTP	ester	-OH	n/a	B10	acetal
667	PBO	ester	-OH	n/a	B10	acetal
668	B11	ester	-OH	n/a	-H	n/a
669	B11	ester	-OEt	ester	-H	n/a
670	B11	ester	DTP	ester	-H	n/a
671	B11	ester	PBO	ester	-H	n/a
672	B11	acetal	-OH	n/a	-H	n/a
673	B11	acetal	-OEt	ester	-H	n/a
674	B11	acetal	DTP	ester	-H	n/a
675	B11	acetal	PBO	ester	-H	n/a
676	B11	amide	-OH	n/a	-H	n/a
677	B11	amide	-OEt	ester	-H	n/a
678	B11	amide	DTP	ester	-H	n/a
679	B11	amide	PBO	ester	-H	n/a
680	-OH	n/a	-OH	n/a	B11	ester
681	-OEt	ester	-OH	n/a	B11	ester
682	DTP	ester	-OH	n/a	B11	ester
683	PBO	ester	-OH	n/a	B11	ester
684	-OH	n/a	-OH	n/a	B11	acetal
685	-OEt	ester	-OH	n/a	B11	acetal
686	DTP	ester	-OH	n/a	B11	acetal
687	PBO	ester	-OH	n/a	B11	acetal
688	B12	ester	-OH	n/a	-H	n/a
689	B12	ester	-OEt	ester	-H	n/a
690	B12	ester	DTP	ester	-H	n/a
691	B12	ester	PBO	ester	-H	n/a
692	B12	acetal	-OH	n/a	-H	n/a
693	B12	acetal	-OEt	ester	-H	n/a
694	B12	acetal	DTP	ester	-H	n/a
695	B12	acetal	PBO	ester	-H	n/a
696	B12	amide	-OH	n/a	-H	n/a
697	B12	amide	-OEt	ester	-H	n/a
698	B12	amide	DTP	ester	-H	n/a
699	B12	amide	PBO	ester	-H	n/a
700	-OH	n/a	-OH	n/a	B12	ester
701	-OEt	ester	-OH	n/a	B12	ester
702	DTP	ester	-OH	n/a	B12	ester

Example #	R1	linkage	R2	linkage	R3	linkage
703	PBO	ester	-OH	n/a	B12	ester
704	-OH	n/a	-OH	n/a	B12	acetal
705	-OEt	ester	-OH	n/a	B12	acetal
706	DTP	ester	-OH	n/a	B12	acetal
707	PBO	ester	-OH	n/a	B12	acetal
708	B13	ester	-OH	n/a	-H	n/a
709	B13	ester	-OEt	ester	-H	n/a
710	B13	ester	DTP	ester	-H	n/a
711	B13	ester	PBO	ester	-H	n/a
712	B13	acetal	-OH	n/a	-H	n/a
713	B13	acetal	-OEt	ester	-H	n/a
714	B13	acetal	DTP	ester	-H	n/a
715	B13	acetal	PBO	ester	-H	n/a
716	B13	amide	-OH	n/a	-H	n/a
717	B13	amide	-OEt	ester	-H	n/a
718	B13	amide	DTP	ester	-H	n/a
719	B13	amide	PBO	ester	-H	n/a
720	-OH	n/a	-OH	n/a	B13	ester
721	-OEt	ester	-OH	n/a	B13	ester
722	DTP	ester	-OH	n/a	B13	ester
723	PBO	ester	-OH	n/a	B13	ester
724	-OH	n/a	-OH	n/a	B13	acetal
725	-OEt	ester	-OH	n/a	B13	acetal
726	DTP	ester	-OH	n/a	B13	acetal
727	PBO	ester	-OH	n/a	B13	acetal
728	B14	amide	-OH	n/a	-H	n/a
729	B14	amide	-OEt	ester	-H	n/a
730	B14	amide	DTP	ester	-H	n/a
731	B14	amide	PBO	ester	-H	n/a
732	B15	amide	-OH	n/a	-H	n/a
733	B15	amide	-OEt	ester	-H	n/a
734	B15	amide	DTP	ester	-H	n/a
735	B15	amide	PBO	ester	-H	n/a
736	B16	amide	-OH	n/a	-H	n/a
737	B16	amide	-OEt	ester	-H	n/a
738	B16	amide	DTP	ester	-H	n/a
739	B16	amide	PBO	ester	-H	n/a
740	B17	amide	-OH	n/a	-H	n/a
741	B17	amide	-OEt	ester	-H	n/a
742	B17	amide	DTP	ester	-H	n/a
743	B17	amide	PBO	ester	-H	n/a
744	B18	amide	-OH	n/a	-H	n/a
745	B18	amide	-OEt	ester	-H	n/a
746	B18	amide	DTP	ester	-H	n/a
747	B18	amide	PBO	ester	-H	n/a
748	B19	amide	-OH	n/a	-H	n/a
749	B19	amide	-OEt	ester	-H	n/a
750	B19	amide	DTP	ester	-H	n/a

Example #	R1	linkage	R2	linkage	R3	linkage
751	B19	amide	PBO	ester	-H	n/a
752	B20	amide	-OH	n/a	-H	n/a
753	B20	amide	-OEt	ester	-H	n/a
754	B20	amide	DTP	ester	-H	n/a
755	B20	amide	PBO	ester	-H	n/a
756	B21	amide	-OH	n/a	-H	n/a
757	B21	amide	-OEt	ester	-H	n/a
758	B21	amide	DTP	ester	-H	n/a
759	B21	amide	PBO	ester	-H	n/a
760	B22	amide	-OH	n/a	-H	n/a
761	B22	amide	-OEt	ester	-H	n/a
762	B22	amide	DTP	ester	-H	n/a
763	B22	amide	PBO	ester	-H	n/a
764	B23	amide	-OH	n/a	-H	n/a
765	B23	amide	-OEt	ester	-H	n/a
766	B23	amide	DTP	ester	-H	n/a
767	B23	amide	PBO	ester	-H	n/a
768	B24	ester	-OH	n/a	-H	n/a
769	B24	ester	-OEt	ester	-H	n/a
770	B24	ester	DTP	ester	-H	n/a
771	B24	ester	PBO	ester	-H	n/a
772	-OH	n/a	-OH	n/a	B24	acetal
773	-OEt	ester	-OH	n/a	B24	acetal
774	DTP	ester	-OH	n/a	B24	acetal
775	PBO	ester	-OH	n/a	B24	acetal

[0070] Some additional compounds of the invention are shown below to illustrate various further aspects of the invention:



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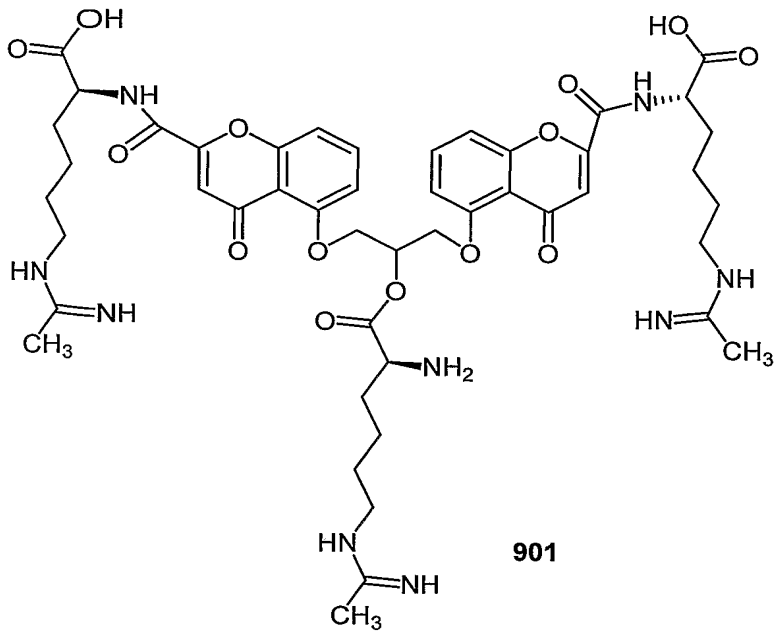
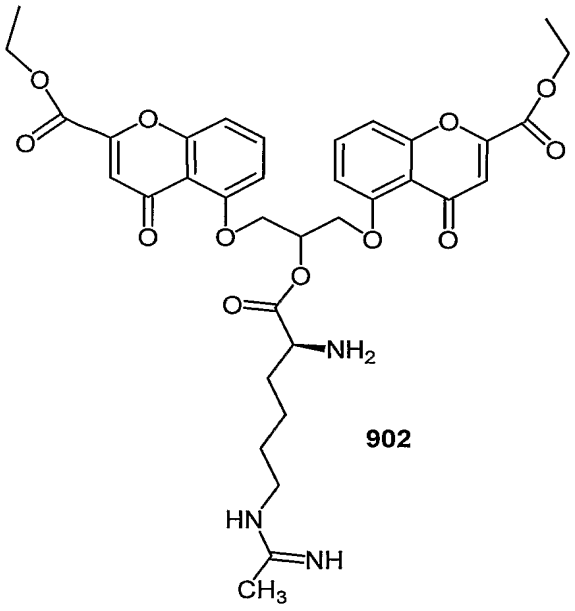


901



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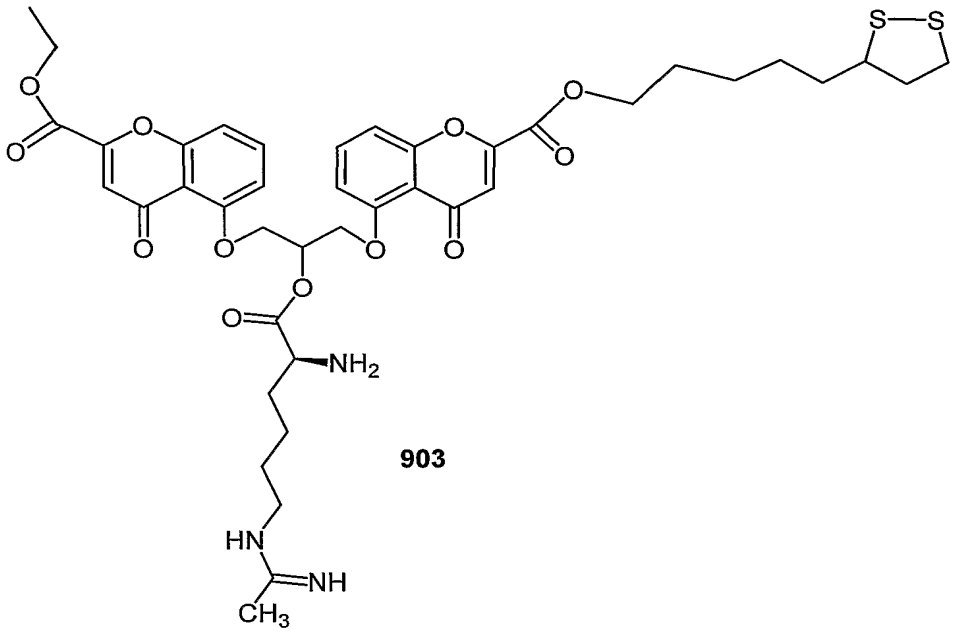

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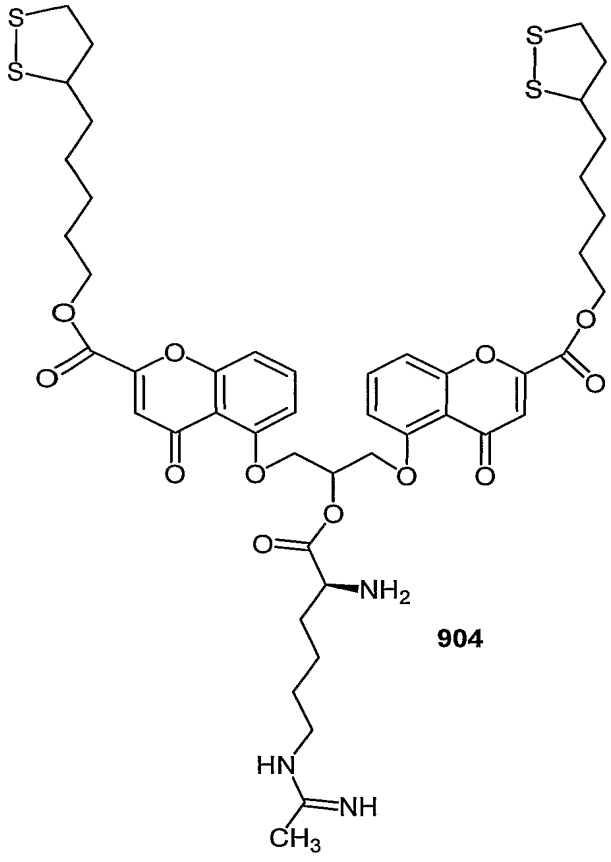

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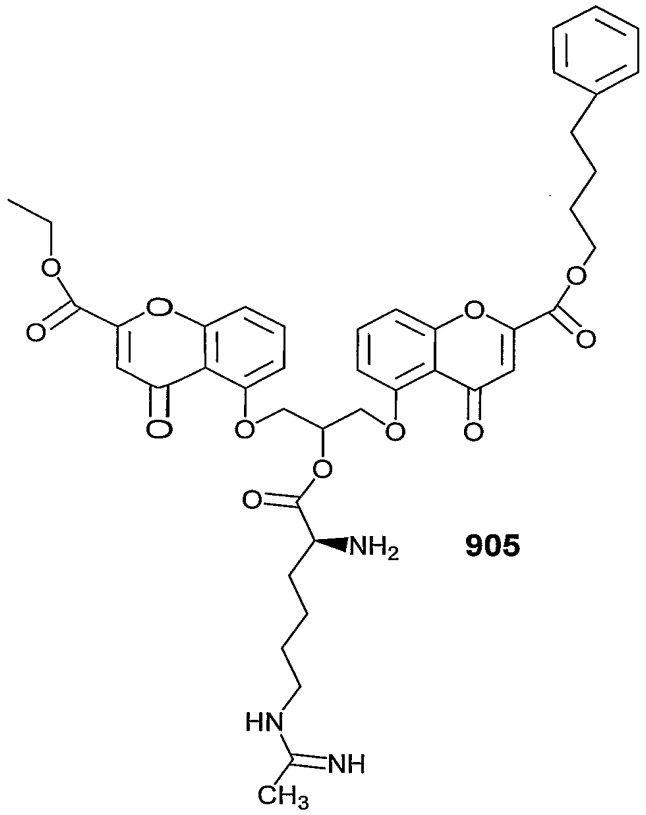

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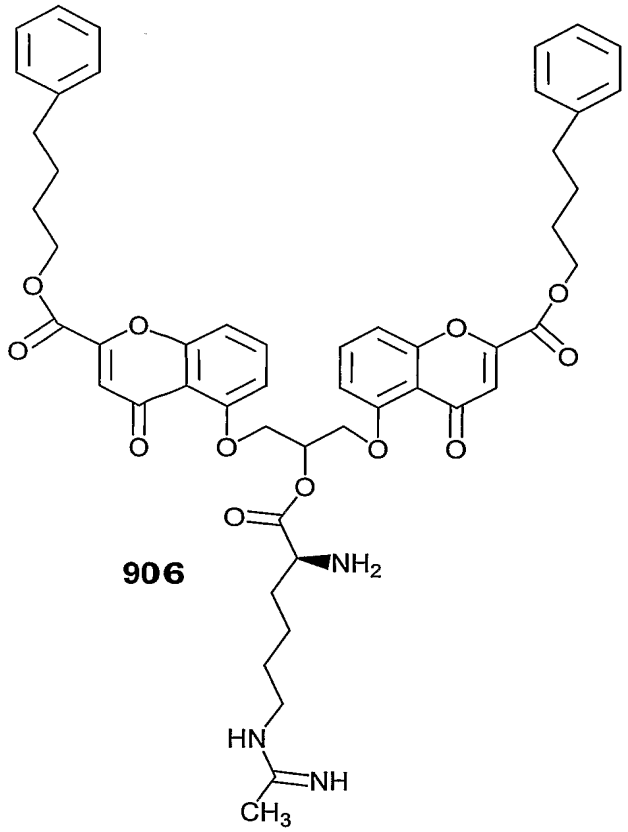
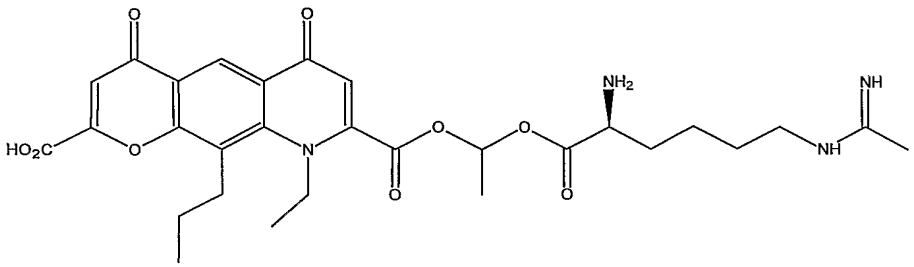


906



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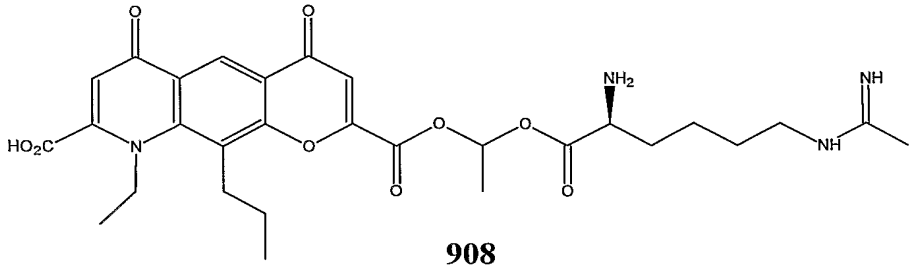

908

[0071] Example **900** illustrates two iNOS inhibitors attached to a single cromolyn core. In this particular example, both iNOS inhibitors are the same, but that is not a requirement of the invention. Similarly, without intending to so restrict the invention, example **901** illustrates three iNOS inhibitors attached to a single cromolyn core. Examples **902-906** illustrate various mixed esters. Examples **907** and **908** illustrate acetals of acetaldehyde (whereas the examples in Tables 1 and 2 show acetals of formaldehyde); both acetals of acetaldehyde and acetals of formaldehyde are within the scope of the invention, and each of the formaldehyde acetal examples in the tables has a corresponding acetaldehyde acetal example.